



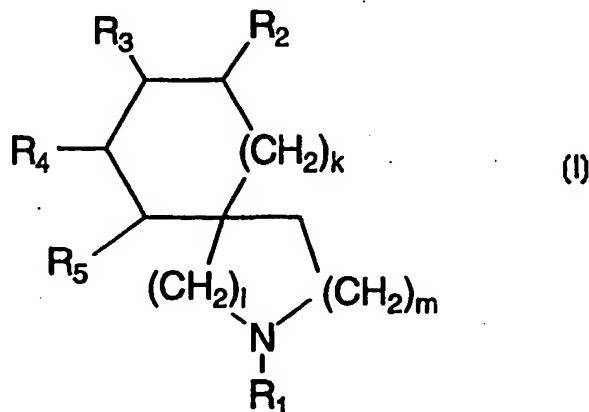
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|--|--|---|--|
| (51) International Patent Classification ⁶ : A61K 31/33, 31/395, 31/41, 31/435, 31/55 | | A1 | (11) International Publication Number: WO 98/25604 |
| | | | (43) International Publication Date: 18 June 1998 (18.06.98) |
| (21) International Application Number: PCT/US97/23093 | | (81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). | |
| (22) International Filing Date: 12 December 1997 (12.12.97) | | | |
| (30) Priority Data: 60/032,890 13 December 1996 (13.12.96) US 60/033,535 20 December 1996 (20.12.96) US 9704366.5 3 March 1997 (03.03.97) GB | | | |
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(54) Title: SPIRO-SUBSTITUTED AZACYCLES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

(57) Abstract

The present invention is directed spiro-substituted azacycles of formula (I) (wherein R₁, R₂, R₃, R₄, R₅, k, l and m are defined herein) which are useful as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, and/or CXCR-4.



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TITLE OF THE INVENTION
SPIRO-SUBSTITUTED AZACYCLES AS MODULATORS OF
CHEMOKINE RECEPTOR ACTIVITY

5 BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation (reviewed in Schall, Cytokine, 3, 165-183 (1991) and Murphy, Rev. Immun., 12, 593-633 (1994)).
10 There are two classes of chemokines, C-X-C (α) and C-C (β), depending on whether the first two cysteines are separated by a single amino acid (C-X-C) or are adjacent (C-C). The α -chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for
15 neutrophils, whereas β -chemokines, such as RANTES, MIP-1 α , MIP-1 β , monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3 and eotaxin are chemotactic for macrophages, T-cells, eosinophils and basophils (Deng, et al., Nature, 381, 661-666 (1996)).

The chemokines bind specific cell-surface receptors
20 belonging to the family of G-protein-coupled seven-transmembrane-domain proteins (reviewed in Horuk, Trends Pharm. Sci., 15, 159-165 (1994)) which are termed "chemokine receptors." On binding their cognate ligands, chemokine receptors transduce an intracellular signal though the associated trimeric G protein, resulting in a rapid increase
25 in intracellular calcium concentration. There are at least seven human chemokine receptors that bind or respond to β -chemokines with the following characteristic pattern: CCR-1 (or "CKR-1" or "CC-CKR-1") [MIP-1 α , MIP-1 β , MCP-3, RANTES] (Ben-Barruch, et al., J. Biol. Chem., 270, 22123-22128 (1995); Beote, et al, Cell, 72, 415-425 (1993)); CCR-
30 2A and CCR-2B (or "CKR-2A"/"CKR-2A" or "CC-CKR-2A"/"CC-CKR-2A") [MCP-1, MCP-3, MCP-4]; CCR-3 (or "CKR-3" or "CC-CKR-3") [eotaxin, RANTES, MCP-3] (Combadiere, et al., J. Biol. Chem., 270, 16491-16494 (1995); CCR-4 (or "CKR-4" or "CC-CKR-4") [MIP-1 α , RANTES, MCP-1] (Power, et al., J. Biol. Chem., 270, 19495-19500 (1995));
35 CCR-5 (or "CKR-5" or "CC-CKR-5") [MIP-1 α , RANTES, MIP-1 β]

(Sanson, et al., Biochemistry, 35, 3362-3367 (1996)); and the Duffy blood-group antigen [RANTES, MCP-1] (Chaudhun, et al., J. Biol. Chem., 269, 7835-7838 (1994)). The β -chemokines include eotaxin, MIP ("macrophage inflammatory protein"), MCP ("monocyte chemoattractant protein") and
5 RANTES ("regulation-upon-activation, normal T expressed and secreted").

Chemokine receptors, such as CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, CXCR-4, have been implicated as being important mediators of inflammatory and immunoregulatory
10 disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. For example, the chemokine receptor CCR-3 plays a pivotal role in attracting eosinophils to sites of allergic inflammation. Accordingly, agents which modulate chemokine receptors would be
15 useful in such disorders and diseases.

A retrovirus designated human immunodeficiency virus (HIV-1) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and
20 peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV.

Certain compounds have been demonstrated to inhibit the replication of HIV, including soluble CD4 protein and synthetic derivatives (Smith, et al., Science, 238, 1704-1707 (1987)), dextran sulfate,
25 the dyes Direct Yellow 50, Evans Blue, and certain azo dyes (U.S. Patent No. 5,468,469). Some of these antiviral agents have been shown to act by blocking the binding of gp120, the coat protein of HIV, to its target, the CD4 glycoprotein of the cell.

Entry of HIV-1 into a target cell requires cell-surface CD4
30 and additional host cell cofactors. Fusin has been identified as a cofactor required for infection with virus adapted for growth in transformed T-cells, however, fusin does not promote entry of macrophagetropic viruses which are believed to be the key pathogenic strains of HIV in vivo. It has recently been recognized that for efficient entry into target
35 cells, human immunodeficiency viruses require the chemokine

receptors CCR-5 and CXCR-4, as well as the primary receptor CD4 (Levy, *N. Engl. J. Med.*, 335(20), 1528-1530 (Nov. 14 1996). The principal cofactor for entry mediated by the envelope glycoproteins of primary macrophage-trophic strains of HIV-1 is CCR5, a receptor for the β -chemokines RANTES, MIP-1 α and MIP-1 β (Deng, et al., *Nature*, 381, 661-666 (1996)). HIV attaches to the CD4 molecule on cells through a region of its envelope protein, gp120. It is believed that the CD-4 binding site on the gp120 of HIV interacts with the CD4 molecule on the cell surface, and undergoes conformational changes which allow it to bind to another cell-surface receptor, such as CCR5 and/or CXCR-4. This brings the viral envelope closer to the cell surface and allows interaction between gp41 on the viral envelope and a fusion domain on the cell surface, fusion with the cell membrane, and entry of the viral core into the cell. Macrophage-tropic HIV and SIV envelope proteins have been shown to induce a signal through CCR-5 on CD4+ cells resulting in chemotaxis of T cells which may enhance the replication of the virus (Weissman, et al., *Nature*, 389, 981-985 (1997)). It has been shown that β -chemokine ligands prevent HIV-1 from fusing with the cell (Dragic, et al., *Nature*, 381, 667-673 (1996)). It has further been demonstrated that a complex of gp120 and soluble CD4 interacts specifically with CCR-5 and inhibits the binding of the natural CCR-5 ligands MIP-1 α and MIP-1 β (Wu, et al., *Nature*, 384, 179-183 (1996); Trkola, et al., *Nature*, 384, 184-187 (1996)).

Humans who are homozygous for mutant CCR-5 receptors which do not serve as co-receptors for HIV-1 in vitro appear to be unusually resistant to HIV-1 infection and are not immunocompromised by the presence of this genetic variant (*Nature*, 382, 722-725 (1996)). Similarly, an alteration in the CCR-2 gene, CCR2-641, can prevent the onset of full-blown AIDS (Smith, et al., *Science*, 277, 959-965 (1997). Absence of CCR-5 appears to confer protection from HIV-1 infection (*Nature*, 382, 668-669 (1996)). An inherited mutation in the gene for CCR5, Delta 32, has been shown to abolish functional expression of the gene and individuals homozygous for the mutation are apparently not susceptible to HIV infection. Other chemokine receptors may be used by some strains of HIV-1 or may be favored by non-sexual routes of

transmission. Although most HIV-1 isolates studied to date utilize CCR-5 or fusin, some can use both as well as the related CCR-2B and CCR-3 as co-receptors (Nature Medicine, 2(11), 1240-1243 (1996)). Nevertheless, drugs targeting chemokine receptors may not be unduly
5 compromised by the genetic diversity of HIV-1 (Zhang, et al., Nature, 383, 768 (1996)). The β -chemokine macrophage-derived chemokine (MDC) has been shown to inhibit HIV-1 infection (Pal, et al., Science, 278 (5338), 695-698 (1997)). The chemokines RANTES, MIP-1 α , MIP-1 β , vMIP-I, vMIP-II, SDF-1 have also been shown to suppress HIV. A
10 derivative of RANTES, (AOP)-RANTES, is a subnanomolar antagonist of CCR-5 function in monocytes (Simmons, et al., Science, 276, 276-279 (1997)). Monoclonal antibodies to CCR-5 have been reported to block infection of cells by HIV in vitro. Accordingly, an agent which could block chemokine receptors in humans who possess normal chemokine
15 receptors should prevent infection in healthy individuals and slow or halt viral progression in infected patients (see Science, 275, 1261-1264 (1997)). By focusing on the host's cellular immune response to HIV infection, better therapies towards all subtypes of HIV may be provided. These results indicate that inhibition of chemokine receptors presents a
20 viable method for the prevention or treatment of infection by HIV and the prevention or treatment of AIDS.

The peptides eotaxin, RANTES, MIP-1 α , MIP-1 β , MCP-1, and MCP-3 are known to bind to chemokine receptors. As noted above, the inhibitors of HIV-1 replication present in supernatants of CD8+ T
25 cells have been characterized as the β -chemokines RANTES, MIP-1 α and MIP-1 β . PCT Patent Publications WO 94/17045 (published August 4, 1994), WO 94/29309 (published December 22, 1994), and WO 96/10568 (published April 11, 1996) disclose certain spiro-substituted azacycles as tachykinin antagonists.

30

SUMMARY OF THE INVENTION

The present invention is directed to compounds which are modulators of chemokine receptor activity and are useful in the prevention or treatment of certain inflammatory and immunoregulatory

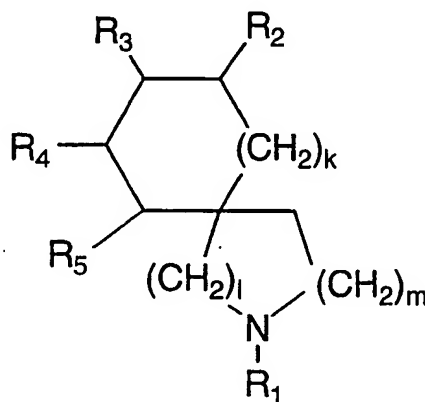
disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which chemokine receptors are involved.

The present invention is further concerned with compounds which inhibit the entry of human immunodeficiency virus (HIV) into target cells and are of value in the prevention of infection by HIV, the treatment of infection by HIV and the prevention and/or treatment of the resulting acquired immune deficiency syndrome (AIDS). The present invention also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the prevention and treatment of AIDS and viral infection by HIV.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of

Formula I:



I

wherein the nitrogen atom expressly shown above is optionally quaternized with C₁₋₄alkyl or phenylC₁₋₄alkyl or is optionally present as the N-oxide (N⁺O⁻), and wherein:

k is 0, 1 or 2;

l and m are each independently 0, 1, 2, 3, 4, or 5, with the proviso that the sum of l + m is equal to 1, 2, 3, 4, or 5;

R₁ is selected from a group consisting of:

- 5 (1) C₁₋₈ linear or branched alkyl, unsubstituted or mono, di, tri or tetra substituted, the substituents independently selected from:
 - (a) hydroxy,
 - (b) oxo,
 - (c) cyano,
 - 10 (d) halogen,
 - (e) trifluoromethyl,
 - (f) phenyl or naphthyl or mono, di or trisubstituted phenyl or naphthyl, the substituents independently selected from:
 - 15 (a) hydroxy,
 - (b) oxo,
 - (c) cyano,
 - (d) halogen,
 - (e) trifluoromethyl
 - 20 (f) -NR₆COR⁷,
 - (g) -NR₆CO₂R⁷,
 - (h) -NR₆CONHR⁷,
 - (i) -NHS(O)_jR⁶,
 - (j) -CONR⁶R⁷,
 - 25 (k) -COR⁶,
 - (l) -CO₂R⁶,
 - (m) -OR⁶,
 - (n) -S(O)_jR⁶,
 - (o) heteroaryl, wherein heteroaryl is as defined below, and
 - 30 (p) phenyl;
 - (g) -NR⁶R⁷, wherein R⁶ and R⁷ are independently selected from:
 - (1) hydrogen,

(2) C₁₋₆ alkyl, or mono or disubstituted C₁₋₆ alkyl,
the substituents independently selected from

- (a) hydroxy,
- (b) oxo,
- (c) cyano,
- (d) halogen,
- (e) trifluoromethyl
- (f) -NR⁸COR⁹, wherein R⁸ and R⁹ selected
from:

(1) hydrogen,
(2) C₁₋₆ alkyl, or mono or di-
substituted C₁₋₆ alkyl, the substituents
independently selected from:

- (a) phenyl,
- (b) hydroxy,
- (c) oxo,
- (d) cyano,
- (e) halogen,
- (f) trifluoromethyl, and

(3) phenyl or mono di or tri-substituted
phenyl, the substituents independently selected
from:

- (a) hydroxy,
- (b) C₁₋₃alkyl,
- (c) cyano,
- (d) halogen,
- (e) trifluoromethyl;
- (g) -NR⁸CO₂R⁹,
- (h) -NR⁸CONHR⁹,
- (i) -NHS(O)_iR⁸,
- (j) -CONR⁸R⁹,
- (k) -COR⁸,
- (l) -CO₂R⁸,
- (m) -OR⁸,

- (n) $-S(O)_jR^8$,
(o) heteroaryl, wherein heteroaryl is as defined below, and
(p) phenyl;
- 5 (3) phenyl or mono di or trisubstituted phenyl, the substituents independently selected from
- (a) hydroxy,
(b) oxo,
(c) cyano,
10 (d) halogen,
(e) trifluoromethyl
(f) $-NR^8COR^9$,
(g) $-NR^8CO_2R^9$,
(h) $-NR^8CONHR^9$,
15 (i) $-NHS(O)_jR^8$,
(j) $-CONR^8R^9$,
(k) $-COR^8$,
(l) $-CO_2R^8$,
(m) $-OR^8$,
20 (n) $-S(O)_jR^8$,
(o) heteroaryl, wherein heteroaryl is as defined below, and
(p) phenyl;
- or R^6 and R^7 are joined together to form a 5-, 6-, or 7-
- 25 membered monocyclic saturated ring containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and in which the ring is unsubstituted or mono or disubstituted, the substituents independently selected from
- 30 (a) hydroxy,
(b) oxo,
(c) cyano,
(d) halogen,
(e) trifluoromethyl

- 5 (f) $-\text{NR}^8\text{COR}^9$,
(g) $-\text{NR}^8\text{CO}_2\text{R}^9$,
(h) $-\text{NR}^8\text{CONHR}^9$,
(i) $-\text{NHS}(\text{O})_j\text{R}^8$,
(j) $-\text{CONR}^8\text{R}^9$,
(k) $-\text{COR}^8$,
(l) $-\text{CO}_2\text{R}^8$,
(m) $-\text{OR}^8$,
(n) $-\text{S}(\text{O})_j\text{R}^8$,
10 (o) heteroaryl, wherein heteroaryl is as
defined below, and
(p) phenyl;
- 15 (h) $-\text{NR}^6\text{COR}^7$,
(i) $-\text{NR}^6\text{CO}_2\text{R}^7$,
(j) $-\text{NR}^6\text{CONHR}^7$,
(k) $-\text{NR}^6\text{S}(\text{O})_j\text{R}^7$, wherein j is 1 or 2,
(l) $-\text{CONR}^6\text{R}^7$,
(m) $-\text{COR}^6$,
(n) $-\text{CO}_2\text{R}^6$,
20 (o) $-\text{OR}^6$,
(p) $-\text{S}(\text{O})_i\text{R}^6$, wherein i is 0, 1, or 2,
(q) $-\text{NR}^6\text{CO}$ -heteroaryl,
(r) $-\text{NR}^6\text{S}(\text{O})_j$ -heteroaryl, and
(s) heteroaryl, wherein heteroaryl is selected from the
25 group consisting of:
(1) benzimidazolyl,
(2) benzofuranyl,
(3) benzooxazolyl,
(4) furanyl,
30 (5) imidazolyl,
(6) indolyl,
(7) isooxazolyl,
(8) isothiazolyl,
(9) oxadiazolyl,

- 5 (10) oxazolyl,
(11) pyrazinyl,
(12) pyrazolyl,
(13) pyridyl,
(14) pyrimidyl,
(15) pyrrolyl,
(16) quinolyl,
(17) tetrazolyl,
10 (18) thiadiazolyl,
(19) thiazolyl,
(20) thienyl,
(21) triazolyl,

15 wherein the heteroaryl is unsubstituted or mono di or
trisubstituted, the substituents independently selected
from

- (a) hydroxy,
(b) oxo,
(c) cyano,
(d) halogen,
20 (e) trifluoromethyl
(f) $-NR_6COR^7$,
(g) $-NR_6CO_2R^7$,
(h) $-NR_6CONHR^7$,
(i) $-NHS(O)_jR^6$,
25 (j) $-CONR^6R^7$,
(k) $-COR^6$,
(l) $-CO_2R^6$,
(m) $-OR^6$,
(n) $-S(O)_jR^6$, and
30 (o) phenyl;

- (2) C₂₋₈ linear or branched alkenyl, unsubstituted or mono, di,
tri or tetra substituted, the substituents independently
selected from:

- 35 (a) hydroxy,

- (b) oxo,
 (c) cyano,
 (d) halogen,
 (e) trifluoromethyl,
 5 (f) phenyl, unsubstituted or mono or disubstituted, the
 substituents independently selected from
- (a) hydroxy,
 (b) oxo,
 (c) cyano,
 10 (d) halogen,
 (e) trifluoromethyl
 (f) $-NR^6COR^7$,
 (g) $-NR^6CO_2R^7$,
 (h) $-NR^6CONHR^7$,
 15 (i) $-NHS(O)_iR^6$,
 (j) $-CONR^6R^7$,
 (k) $-COR^6$,
 (l) $-CO_2R^6$,
 (m) $-OR^6$,
 20 (n) $-S(O)_jR^6$,
 (o) heteroaryl, wherein heteroaryl is as
 defined below, and
 (p) phenyl;
- (g) $-NR^6R^7$,
 25 (h) $-NR^6COR^7$,
 (i) $-NR^6CO_2R^7$,
 (j) $-NR^6CONHR^7$,
 (k) $-NR^6S(O)_jR^7$, wherein j is 1 or 2,
 (l) $-CONR^6R^7$,
 30 (m) $-COR^6$,
 (n) $-CO_2R^6$,
 (o) $-OR^6$,
 (p) $-S(O)_iR^6$, wherein i is 0, 1, or 2,
 (q) $-NR^6CO$ -heteroaryl,
 35 (r) $-NR^6S(O)_j$ -heteroaryl, and

(s) heteroaryl, wherein heteroaryl is defined above;

(3) C₂₋₈ alkynyl, unsubstituted or mono, di tri or tetra substituted, the substituents independently selected from;

5

(a) hydroxy,

(b) oxo,

(c) cyano,

(d) halogen,

(e) trifluoromethyl,

10

(f) phenyl, unsubstituted or mono or disubstituted, the substituents independently selected from

(a) hydroxy,

(b) oxo,

(c) cyano,

15

(d) halogen,

(e) trifluoromethyl

(f) -NR⁶COR⁷,

(g) -NR⁶CO₂R⁷,

(h) -NR⁶CONHR⁷,

20

(i) -NHS(O)_jR⁶,

(j) -CONR⁶R⁷,

(k) -COR⁶,

(l) -CO₂R⁶,

(m) -OR⁶,

25

(n) -S(O)_jR⁶,

(o) heteroaryl, wherein heteroaryl is as defined below, and

(p) phenyl;

(g) -NR⁶R⁷,

30

(h) -NR⁶COR⁷,

(i) -NR⁶CO₂R⁷,

(j) -NR⁶CONHR⁷,

(k) -NR⁶S(O)_jR⁷, wherein j is 1 or 2,

(l) -CONR⁶R⁷,

35

(m) -COR⁶,

- (n) $-\text{CO}_2\text{R}^6$,
 (o) $-\text{OR}^6$,
 (p) $-\text{S}(\text{O})_i\text{R}^6$, wherein i is 0, 1, or 2,
 (q) $-\text{NR}^6\text{CO}$ -heteroaryl,
 5 (r) $-\text{NR}^6\text{S}(\text{O})_j$ -heteroaryl, and
 (s) heteroaryl, wherein heteroaryl is defined above;
 wherein the nitrogen of definitions $-\text{NR}^6\text{R}^7$ above is optionally
 quaternized with C_{1-4} alkyl or phenyl C_{1-4} alkyl or is optionally present as
 the N-oxide (N^+O^-);

10

R^2 , R^3 , R^4 , and R^5 are independently selected from the group consisting
 of:

- (1) hydrogen;
 (2) hydroxy;
 15 (3) oxo; and
 (4) $-\text{NR}^6\text{R}^7$, wherein the nitrogen is optionally quaternized
 with C_{1-4} alkyl or phenyl C_{1-4} alkyl or is present as the N-
 oxide,

or R^2 and R^3 , or R^3 and R^4 , together form a carbon-carbon bond,
 20 or R^2 and R^3 , or R^3 and R^4 , or R^4 and R^5 are joined to form
 an aryl or heteroaryl, wherein heteroaryl is as defined above and aryl is
 phenyl or naphthyl, wherein the phenyl or naphthyl is unsubstituted or
 mono di or trisubstituted, the substituents independently selected from:

- (a) C_{1-6} linear or branched alkyl,
 25 (b) C_{2-6} linear or branched alkenyl,
 (c) C_{2-6} linear or branched alkynyl,
 (d) cyano,
 (e) halogen,
 (f) trifluoromethyl,
 30 (g) C_{1-6} alkoxy,
 (f) $-\text{NR}^6\text{R}^7$,
 (g) $-\text{NR}^6\text{COR}^7$,
 (h) $-\text{NR}^6\text{CO}_2\text{R}^7$,
 (i) $-\text{NR}^6\text{CONHR}^7$,

(j) $-\text{NR}_6\text{S}(\text{O})_j-\text{R}_7$

(k) $-\text{CONR}^6\text{R}^7,$

(l) $-\text{COR}^6,$

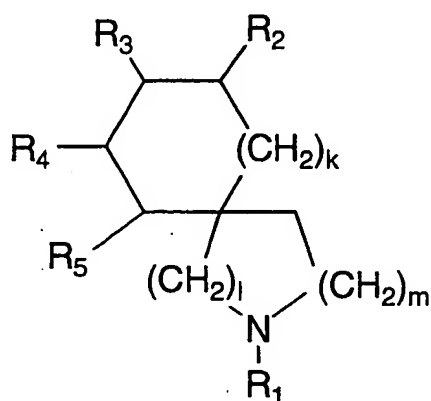
(m) $-\text{CO}_2\text{R}^6,$

5 (n) $-\text{S}(\text{O})_i\text{R}_6;$

X is carbon, or $\text{X}-\text{R}^5$ is oxygen or $\text{S}-(\text{O})_i;$

and pharmaceutically acceptable salts thereof.

In an alternative embodiment, the invention is directed to
10 compounds of the Formula I:



I

wherein the nitrogen atom expressly shown above is optionally
quaternized with C_{1-4} alkyl or phenyl C_{1-4} alkyl or is optionally present as
15 the N-oxide (N^+O^-), and wherein:

k is 0, 1 or 2;

l and m are each independently 0, 1, 2, 3, 4, or 5, with the proviso that the
sum of $l + m$ is equal to 1, 2, 3, 4, or 5;

R_1 is selected from a group consisting of:

- 20 (1) hydrogen,
(2) linear or branched C_{1-8} alkyl, linear or branched C_{2-8}
alkenyl, or linear or branched C_{2-8} alkynyl, wherein the C_{1-8}
alkyl, C_{2-8} alkenyl or C_{2-8} alkynyl is optionally mono, di,
tri or tetra substituted, the substituents independently
25 selected from:
(a) hydroxy,

- (b) oxo,
(c) cyano,
(d) halogen, wherein halogen is selected from:
Br, Cl, I, and F,
5 (e) trifluoromethyl,
(f) phenyl or naphthyl or mono, di or trisubstituted
phenyl or naphthyl, the substituents independently selected
from
(1') hydroxy,
10 (2') oxo,
(3') phenyl,
(4') C₁₋₃alkyl,
(5') cyano,
(6') halogen,
15 (7') trifluoromethyl,
(8') -NR₆COR₇, wherein R₆ and R₇ are
independently selected from:
(a') hydrogen,
(b') C₁₋₆ alkyl, or mono or disubstituted C₁₋₆ alkyl,
20 the substituents independently selected from:
(1'') phenyl,
(2'') hydroxy,
(3'') oxo,
(4'') cyano,
25 (5'') halogen,
(6'') trifluoromethyl,
(c') phenyl or naphthyl or mono di or trisubstituted
phenyl or naphthyl, the substituents independently
selected from:
30 (1'') hydroxy,
(2'') C₁₋₃alkyl,
(3'') cyano,
(4'') halogen,
(5'') trifluoromethyl,
35 (d') C₁₋₃alkyloxy,

or R₆ and R₇ are joined together with the nitrogen to which they are attached to form a 5-, 6-, or 7-membered monocyclic saturated ring containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and in which the ring is unsubstituted or mono or disubstituted, the substituents independently selected from

- (1") hydroxy,
- (2") oxo,
- (3") cyano,
- (4") halogen,
- (5") trifluoromethyl,
- (9') -NR₆CO₂R₇,
- (10') -NR₆CONHR₇,
- (11') -NR₆S(O)_jR₇, wherein j is 1 or 2,
- (12') -CONR₆R₇,
- (13') -COR₆,
- (14') -CO₂R₆,
- (15') -OR₆,
- (16') -S(O)_iR₆, wherein i is 0, 1, or 2,
- (17') heteroaryl, wherein heteroaryl is selected from the group consisting of:

- (1") benzimidazolyl,
- (2") benzofuranyl,
- (3") benzooxazolyl,
- (4") furanyl,
- (5") imidazolyl,
- (6") indolyl,
- (7") isooxazolyl,
- (8") isothiazolyl,
- (9") oxadiazolyl,
- (10") oxazolyl,
- (11") pyrazinyl,
- (12") pyrazolyl,

- 5 (13") pyridyl,
(14") pyrimidyl,
(15") pyrrolyl,
(16") quinolyl,
(17") tetrazolyl,
(18") thiadiazolyl,
(19") thiazolyl,
(20") thienyl, and
(21") triazolyl,

10 wherein the heteroaryl is unsubstituted or mono di or trisubstituted, the substituents independently selected from:

- 15 (a") hydroxy,
(b") oxo,
(c") cyano,
(d") halogen,
(e") trifluoromethyl,

- 20 (g) -NR₆R₇,
(h) -NR₆COR₇,
(i) -NR₆CO₂R₇,
(j) -NR₆CONHR₇,
(k) -NR₆S(O)_jR₇,
(l) -CONR₆R₇,
(m) -COR₆,
25 (n) -CO₂R₆,
(o) -OR₆,
(p) -S(O)_iR₆,

(q) heteroaryl, wherein heteroaryl is defined above;

30 wherein the nitrogen of definition -NR₆R₇ above is optionally quaternized with C₁₋₄alkyl or phenylC₁₋₄alkyl or is optionally present as the N-oxide (N⁺O⁻);

35 R², R³, R⁴, and R⁵ are independently selected from the group consisting of:

- (1) hydrogen;
(2) hydroxy;
(3) oxo; and
(4) -NR₆R₇ or -NR₆C(O)-NR₆R₇, wherein the nitrogen of -
5 NR₆R₇ is optionally quaternized with C₁₋₄alkyl or
phenylC₁₋₄alkyl or is optionally present as the N-oxide,

or R² and R³, or R³ and R⁴, together form a carbon-carbon bond,
or R² and R³, or R³ and R⁴, or R⁴ and R⁵ are joined to form
10 a ring selected from the group consisting of:

- (a) benzimidazolyl,
(b) benzofuranyl,
(c) benzooxazolyl,
(d) furanyl,
15 (e) imidazolyl,
(f) indolyl,
(g) isooxazolyl,
(h) isothiazolyl,
(i) naphthyl,
20 (j) oxadiazolyl,
(k) oxazolyl,
(l) phenyl
(m) pyrazinyl,
(n) pyrazolyl,
25 (o) pyridyl,
(p) pyrimidyl,
(q) pyrrolyl,
(r) quinolyl,
(s) thiadiazolyl,
30 (t) thiazolyl,
(u) thienyl, and
(v) triazolyl,

and wherein the ring is unsubstituted, mono, di or tri
substituted, the substituents selected from:

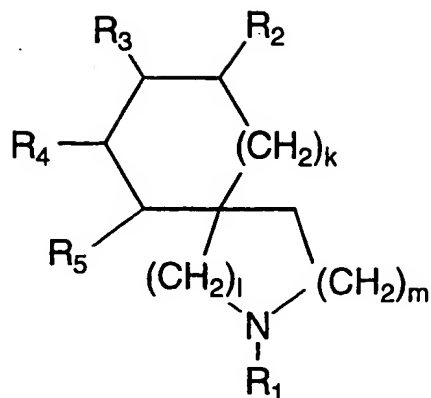
- 5 (1') C₁₋₆ linear or branched alkyl, unsubstituted or
mono or disubstituted, the substituents being
selected from hydrogen and hydroxy,
(2') C₂₋₆ linear or branched alkenyl,
(3') hydroxy
(4') oxo
(5') -OR₆,
(6') halogen,
(7') trifluoromethyl,
10 (8') nitro,
(9') cyano,
(10') -NR⁶R⁷,
(11') -NR⁶COR⁷,
(12') -NR₆CO₂R⁷,
15 (13') -NR₆CONHR⁷,
(14') -NR₆S(O)_j-R⁷
(15') -CONR⁶R⁷,
(16') -COR⁶,
(17') -CO₂R⁶,
20 (18') -S(O)_iR₆, and
(19') heteroaryl, wherein heteroaryl is defined
above;

X is carbon, or X-R⁵ is oxygen or S-(O)_i;

and pharmaceutically acceptable salts thereof.

25

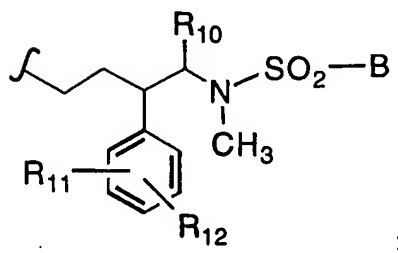
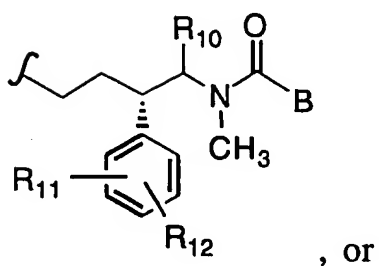
Preferred compound for use in the present invention
include those of Formula II:



II

wherein k is 0 or 1;
the sum of l + m is 3;

5 R₁ is:



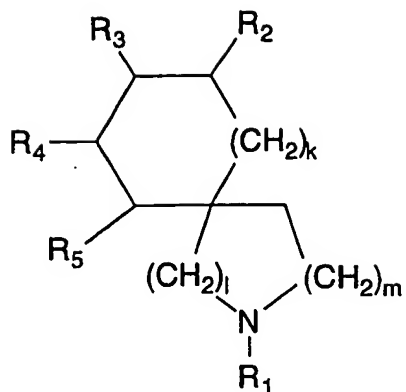
R₂ and R₃ are independently selected from: hydrogen, hydroxy, oxo, or -NR₆C(O)R₇R₈,

10 wherein R₆, R₇ and R₈ are independently selected from:

- (a) hydrogen,
- (b) C₁-6 alkyl, which is unsubstituted or mono or disubstituted,
wherein the substituents on alkyl are independently
selected from: hydroxy, halo, trifluoromethyl, C₁-3alkyl,
15 and phenyl;

- (c) phenyl, unsubstituted or mono or disubstituted, the substituents on phenyl are independently selected from: hydroxy, halo, trifluoromethyl, C₁₋₃alkyl and phenyl;
- 5 B is selected from:
- (a) phenyl, naphthyl, mono di or trisubstituted phenyl, and mono di or trisubstituted naphthyl, wherein the substituents on phenyl or naphthyl are independently selected from: chloro, methyl, phenyl and CF₃;
- 10 (b) -CH₂-phenyl, or mono or disubstituted -CH₂-phenyl, wherein the substituents on phenyl are independently selected from: fluoro, chloro, methyl, phenyl or CF₃;
- (c) pyridyl, or mono, di or trisubstituted pyridyl, wherein the substituents on pyridyl are independently selected from:
- 15 chloro, methyl, phenyl or CF₃;
- (d) thiophene, or mono or disubstituted thiophene, wherein the substituents on thiophene are independently selected from: chloro, methyl, phenyl or CF₃;
- 20 R₄ and R₅ are joined together to form a ring selected from: thiophene or substituted phenyl, wherein the substituent on phenyl is selected from:
- (a) hydrogen,
- (b) CH₃O-,
- 25 (c) CH₃SO₂NH-, and
- (d) CH₃SO₂-;
- R₁₀ is selected from: hydrogen, C₁₋₃alkyl, and phenyl;
- R₁₁ and R₁₂ are independently selected from:
- hydrogen, halogen, methyl, phenyl or CF₃;
- 30 and pharmaceutically acceptable salts thereof.

More preferred compounds for use in the present invention include the compounds of Formula II:



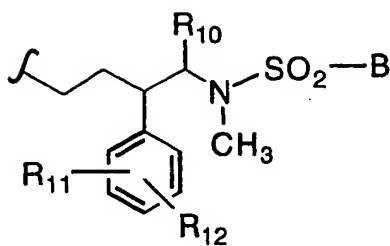
II

wherein:

k is 0 or 1;

5 the sum of l + m is 3;

R₁ is:



10 R₂ and R₃ are independently selected from:
hydrogen, hydroxy, oxo, and -NR₆C(O)R₆R₇;

B is selected from:

15 phenyl, mono or disubstituted phenyl, naphthyl, mono or
disubstituted naphthyl, thiophene, and monosubstituted
thiophene wherein the substituent on phenyl, naphthyl or
thiophene is selected from: CF₃, CH₃, Cl, F, and Br;

20 R₄ and R₅ are joined together to form a ring selected from:
thiophene and substituted phenyl, wherein the substituent on
phenyl is selected from:
(a) hydrogen,

- (b) $\text{CH}_3\text{O}-$,
- (c) $\text{CH}_3\text{SO}_2\text{NH}-$, and
- (d) CH_3SO_2- ;

5 R_{10} is hydrogen, C_{1-3} alkyl or phenyl;

R_{11} and R_{12} are independently selected from:

hydrogen, chloro, methyl, phenyl or CF_3 ;

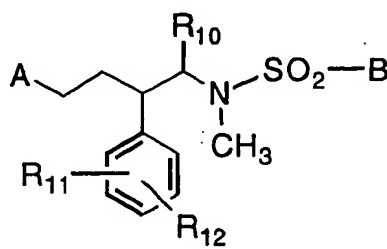
and pharmaceutically acceptable salts thereof.

10

Even more preferred compounds for use in the present invention include those of Formula II wherein B is unsubstituted phenyl, 3-chlorophenyl, 3-fluorophenyl or unsubstituted thiophene.

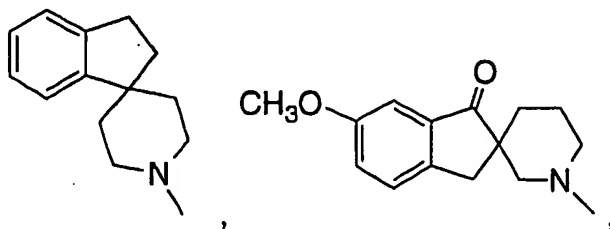
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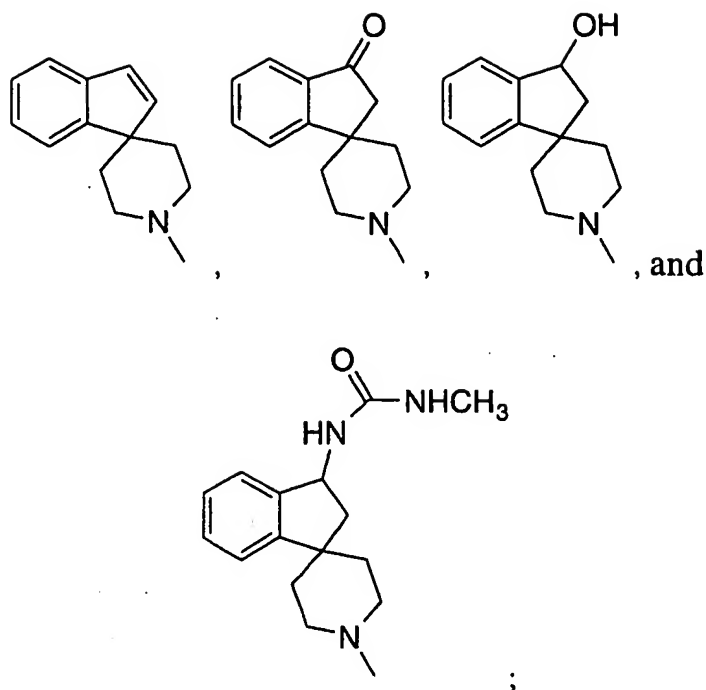
Even more preferred compounds for use in the present invention include those of the Formula III:



III

20 wherein A is selected from:





B is selected from:

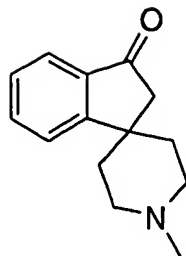
- phenyl, mono or disubstituted phenyl, thiophene, and
 5 monosubstituted thiophene wherein the substituent on
 phenyl or thiophene is selected from:
 CF₃, CH₃, Cl, F, and Br;

R₁₁ and R₁₂ are independently selected from:

- 10 hydrogen, chloro, methyl, phenyl or CF₃;
 and pharmaceutically acceptable salts thereof.

Even more preferred compounds for use in the present invention include those of Formula III wherein B is unsubstituted phenyl, 3-chlorophenyl, 3-fluorophenyl or unsubstituted thiophene.

- 15 Even more preferred compounds for use in the present invention include those of Formula III wherein A is:



Even more preferred compounds for use in the present invention include those of Formula III wherein R₁₁ and R₁₂ are chloro.

- Exemplifying the present invention is the use of a
 5 compound selected from the group consisting of:
- 1'-(3(S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)spiro(1H-indene-1,4'-piperidine);
 - 1'-(3(S)-(3,4-dichlorophenyl)-4-((N-methyl)-3,5-bis(trifluoromethyl)benzamidobutyl)spiro(1H-indene-1,4'-piperidine);
 - 10 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)-3,4-dihydro-4-hydroxy-6-methoxy-spiro[2H-1-benzopyran-2,3'-piperidine];
 - 1'-(3(S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)-3,4-dihydro-4-hydroxy-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperidine];
 - 15 1'-(3(S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)spiro(indane-1,4'-piperidine);
 - 1'-(1-oxo-(3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamidobutyl)spiro(1H-indene-1,4'-piperidine);
 - 1'-(3(S)-(3,4-dichlorophenyl)-(4)-((N-methyl)benzamido)pentyl)spiro(1H-indene-1,4'-piperidine);
 - 20 1'-((2)-((3S)-(3,4-dichlorophenyl)-5-(N-methyl)benzamido)pentyl)spiro(1-indane-1,4'-piperidine);
 - 1'-(3(S)-(3,4-dichlorophenyl)-(4)-((N-methyl)benzamido)octyl)spiro(1H-indene-1,4'-piperidine);
 - 1'-(4)-((3S)-(3,4-dichlorophenyl)-1-(N-methyl)benzamido)octyl)spiro(1H-indene-1,4'-piperidine);
 - 25 1'-(3(S)-(3,4-dichlorophenyl)-4-((N-methyl)benzenesulfonamidobutyl) spiro[1H-indene-1,4'-piperidine];
 - 1'-(3(S)-(3,4-dichlorophenyl)-4-((N-methyl)furan-2-carboxamidobutyl) spiro[1H-indene-1,4'-piperidine];

- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)phenoxy-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)phenyl-aminocarboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 5 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)pyridine-2-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)pyridine-3-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 10 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)pyridine-4-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)benzo-thiophene-2-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)thiophene-2-acetamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 15 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)thiophene-3-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(3-methyl-thiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(5-methyl-thiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 20 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(5-chloro-thiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(2,3-dibromo-thiophene-5-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 25 1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butoxycarbonyl(methyl-amino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dichloro)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-chloro)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 30 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-trifluoromethyl)-benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-isopropoxy)-benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);

- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-isopropoxy)-phenylacetyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(4-t-butyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 5 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-phenyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(1-naphthoyl-(methylamino))butyl)-spiro(1H-indene-1,4'-piperidine);
- 10 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-naphthoyl-(methylamino))butyl)-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-methyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(4-methyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 15 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-methyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,3-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 20 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,4-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,5-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 25 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,4-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(trifluoroacetyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butylcarbonyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 30 1'-[3-(S)-(3,4-dichlorophenyl)-4-(1-adamantanecarbonyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(cyclohexanecarbonyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);

- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-methyl)benzoyl-(methylamino))butyl]-spiro[indane-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[indane-1,4'-piperidine];
- 5 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-bis(trifluoromethyl)benzoyl-(methylamino))butyl)-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 10 1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butoxycarbonyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dichloro)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 15 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-chloro-5-methyl)benzoyl(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-fluoro-5-methyl)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(1-naphthoyl(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 20 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-hydroxy)indane)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-acetyloxy)indane)-1,4'-piperidine];
- 25 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-methylamino-carbonyl-amino)indane-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-bis(trifluoromethyl)benzoyl-(methylamino))butyl)-spiro[(3-ethoxycarbonyl)indane)-1,4'-piperidine];
- 30 1'-[3-(S)-(3,4-dichlorophenyl)-4-(benzoyl(methylamino))-butyl]-spiro[(3-ethoxycarbonyl)indane)-1,4'-piperidine];
- 1'-((3-(S)-(3-chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(indan-1-one-3,4'-piperidine);

1'-(3-((S)-(3-chlorophenyl))-4-(N-(phenylsulfonyl)(methyl-
amino))-butyl)-spiro(1-hydroxyindane-3,4'-piperidine);

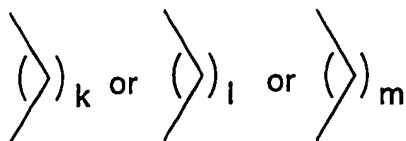
1'-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methyl-
amino))-butyl)-spiro(indane-1,4'-piperidine); and

5 1'-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methyl-
amino))-butyl)-spiro(6-methoxyindan-1-one-2,4'-piperidine);

and pharmaceutically acceptable salts thereof.

The subject compounds are useful in a method of
modulating chemokine receptor activity in a patient in need of such
10 modulation comprising the administration of an effective amount of the
compound.

As is clear from the examples and schemes, the
designation:



15 in formula I is interchangeable with $(\text{CH}_2)_k$ or $(\text{CH}_2)_l$ or $(\text{CH}_2)_m$
respectively. As appreciated by those of skill in the art, halo as used
herein are intended to include chloro, fluoro, bromo and iodo.

The present invention is directed to the use of the foregoing
spiro-substituted azacycles as modulators of chemokine receptor activity.
20 In particular, these compounds are useful as modulators of the
chemokine receptors, including CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-
3, CCR-4, CCR-5, CXCR-3, and/or CXCR-4.

The present invention is further directed to the use of
compounds of this general structure which are disclosed as being
25 antagonists of neurokinin receptors. Such compounds are disclosed, for
example, in: U.S. Patent No. 5,317,020; U.S. Patent No. 5,534,525; U.S.
Patent No. 5,350,852; U.S. Patent No. 5,411,971; U.S. Patent No. 5,446,052;
U.S. Patent No. 5,560,700; EP 0 559 538, Sep. 8, 1993; EP 0 591 040, Apr. 6,
1994; EP 0 698 601, Feb. 28, 1996; EP 0 625 509, Nov. 23, 1994; EP 0 630 887,
30 Dec. 28, 1994; EP 0 680 962, Nov. 8, 1995; EP 0 709 375, May 1, 1996; EP 0
709 376, May 1, 1996; EP 0 723 959, Jul. 31, 1996; EP 0 739 891; WO

94/10146, May 11, 1994; WO 94/17045, Aug. 4, 1994; WO 94/26735, Nov. 24, 1994; WO 94/29309, Dec. 22, 1994; WO 95/05377, Feb. 23, 1995; WO 95/12577, May 11, 1995; WO 95/15961, Jun. 15, 1995; WO 95/16682, Jun. 22, 1995; WO 95/21187; WO 95/26335, Oct. 5, 1995; WO 95/26338, Oct. 5, 1995; WO 95/35279; WO 96/06094, Feb. 29, 1996; WO 96/10568, Apr. 11, 1996; WO 96/23787, Aug. 8, 1996; WO 96/24582, Aug. 15, 1996; WO 96/28441; and WO 96/32385. Accordingly, the present invention embraces the use of a compound disclosed in these publications as a modulator of chemokine receptor activity.

10 The utility of the compounds in accordance with the present invention as modulators of chemokine receptor activity may be demonstrated by methodology known in the art, such as the assay for CCR-1 and/or CCR-5 binding as disclosed by Van Riper, et al., J. Exp. Med., 177, 851-856 (1993), and the assay for CCR-2 and/or CCR-3 binding
15 as disclosed by Daugherty, et al., J. Exp. Med., 183, 2349-2354 (1996). Cell lines for expressing the receptor of interest include those naturally expressing the receptor, such as EOL-3 or THP-1, or a cell engineered to express a recombinant receptor, such as CHO, RBL-2H3, HEK-293. For example, a CCR3 transfected AML14.3D10 cell line has been placed on
20 restricted deposit with American Type Culture Collection in Rockville, Maryland as ATCC No. CRL-12079, on April 5, 1996. The utility of the compounds in accordance with the present invention as inhibitors of the spread of HIV infection in cells may be demonstrated by methodology known in the art, such as the HIV quantitation assay disclosed by
25 Nunberg, et al., J. Virology, 65 (9), 4887-4892 (1991).

 In particular, the compounds of the following examples had activity in binding to either the CCR-5 receptor or the CCR-3 receptor in the aforementioned assays. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor
30 activity.

 Mammalian chemokine receptors provide a target for interfering with or promoting eosinophil and/or lymphocyte function in a mammal, such as a human. Compounds which inhibit or promote chemokine receptor function, are particularly useful for modulating
35 eosinophil and/or lymphocyte function for therapeutic purposes.

Accordingly, the present invention is directed to compounds which are useful in the prevention and/or treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis.

For example, an instant compound which inhibits one or more functions of a mammalian chemokine receptor (e.g., a human chemokine receptor) may be administered to inhibit (i.e., reduce or prevent) inflammation. As a result, one or more inflammatory processes, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, is inhibited. For example, eosinophilic infiltration to inflammatory sites (e.g., in asthma) can be inhibited according to the present method.

Similarly, an instant compound which promotes one or more functions of a mammalian chemokine receptor (e.g., a human chemokine) is administered to stimulate (induce or enhance) an inflammatory response, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, resulting in the beneficial stimulation of inflammatory processes. For example, eosinophils can be recruited to combat parasitic infections.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

Diseases and conditions associated with inflammation and infection can be treated using the method of the present invention. In a preferred embodiment, the disease or condition is one in which the actions of eosinophils and/or lymphocytes are to be inhibited or promoted, in order to modulate the inflammatory response.

Diseases or conditions of humans or other species which can be treated with inhibitors of chemokine receptor function, include,

but are not limited to: inflammatory or allergic diseases and conditions, including respiratory allergic diseases such as asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic
5 eosinophilic pneumonia), delayed-type hypersensitivity, interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses,
10 drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including
15 allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria;
20 vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinophilic myositis, eosinophilic fasciitis; cancers with leukocyte infiltration of the skin or organs. Other diseases or conditions in which undesirable inflammatory responses are to be inhibited can be treated, including, but not limited to, reperfusion injury, atherosclerosis, certain
25 hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock), polymyositis, dermatomyositis.

Diseases or conditions of humans or other species which can be treated with promoters of chemokine receptor function, include, but are not limited to: immunosuppression, such as that in individuals
30 with immunodeficiency syndromes such as AIDS, individuals undergoing radiation therapy, chemotherapy, therapy for autoimmune disease or other drug therapy (e.g., corticosteroid therapy), which causes immunosuppression; immunosuppression due congenital deficiency in receptor function or other causes; and infectious diseases,
35 such as parasitic diseases, including, but not limited to helminth

infections, such as nematodes (round worms); (Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis, filariasis); trematodes (flukes) (Schistosomiasis, Clonorchiasis), cestodes (tape worms) (Echinococcosis, Taeniasis saginata, Cysticercosis); visceral worms, visceral larva migrans (e.g., Toxocara), eosinophilic gastroenteritis (e.g., Anisaki spp., *Phocanema ssp.*), cutaneous larva migrans (*Ancylostoma braziliense*, *Ancylostoma caninum*).

The compounds of the present invention are accordingly useful in the prevention and treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases.

In another aspect, the instant invention may be used to evaluate putative specific agonists or antagonists of chemokine receptors, including CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, and CXCR-4. Accordingly, the present invention is directed to the use of these compounds in the preparation and execution of screening assays for compounds which modulate the activity of chemokine receptors. For example, the compounds of this invention are useful for isolating receptor mutants, which are excellent screening tools for more potent compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other compounds to chemokine receptors, e.g., by competitive inhibition. The compounds of the instant invention are also useful for the evaluation of putative specific modulators of the chemokine receptors, including CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, and CXCR-4. As appreciated in the art, thorough evaluation of specific agonists and antagonists of the above chemokine receptors has been hampered by the lack of availability of non-peptidyl (metabolically resistant) compounds with high binding affinity for these receptors. Thus the compounds of this invention are commercial products to be sold for these purposes.

The present invention is further directed to a method for the manufacture of a medicament for modulating chemokine receptor activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The present invention is further directed to the use of these compounds in the prevention or treatment of infection by a retrovirus, in particular, the human immunodeficiency virus (HIV) and the treatment of, and delaying of the onset of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery. In addition, a compound of the present invention may be used for the prevention of infection by HIV and the prevention of AIDS, such as in post-coital prophylaxis or in the prevention of maternal transmission of the HIV virus to a fetus or a child upon birth.

In a preferred aspect of the present invention, a subject compound may be used in a method of inhibiting the binding of a human immunodeficiency virus to a chemokine receptor, such as CCR-5 and/or CXCR-4, of a target cell, which comprises contacting the target cell with an amount of the compound which is effective at inhibiting the binding of the virus to the chemokine receptor.

The subject treated in the methods above is a mammal, preferably a human being, male or female, in whom modulation of chemokine receptor activity is desired. "Modulation" as used herein is intended to encompass antagonism, agonism, partial antagonism and/or partial agonism. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified

amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

5 The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

10 Combined therapy to modulate chemokine receptor activity and thereby prevent and treat inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis, and those pathologies noted above is illustrated by the combination of the compounds of this invention and other compounds which are known for such utilities.

15 For example, in the treatment or prevention of inflammation, the present compounds may be used in conjunction with an antiinflammatory or analgesic agent such as an opiate agonist, a lipoxigenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an
20 interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, aspirin, codiene, fentanyl, ibuprofen,
25 indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the instant compounds may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as
30 phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antiitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine. Likewise, compounds of the
35 present invention may be used in combination with other drugs that are

used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention. Examples of other active ingredients that may be combined with a compound of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists such as those described in US 5,510,332, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, WO96/01644, WO96/06108, WO95/15973 and WO96/31206; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β 2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen,

indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, 5 oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic acid, 10 sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) other antagonists of the chemokine receptors, especially CCR-1, CCR-2, CCR-3 and CCR-5; (j) cholesterol lowering agents such as HMG-CoA 15 reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzaifibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides 20 (metformin), α -glucosidase inhibitors (acarbose) and glitazones (troglitazone and pioglitazone); (l) preparations of interferon beta (interferon beta-1 α , interferon beta-1 β); (m) other compounds such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer 25 chemotherapeutic agents. The weight ratio of the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID 30 the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active 35 ingredient should be used.

The present invention is further directed to combinations of the present compounds with one or more agents useful in the prevention or treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or vaccines known to those of ordinary skill in the art.

ANTIVIRALS

10

| <u>Drug Name</u> | <u>Manufacturer</u> | <u>Indication</u> |
|--------------------|---------------------------------|---|
| 097 | Hoechst/Bayer | HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase (RT) inhibitor) |
| 141 W94 | Glaxo Wellcome | HIV infection, AIDS, ARC (protease inhibitor) |
| 1592U89 | Glaxo Wellcome | HIV infection, AIDS, ARC (protease inhibitor) |
| Abacavir (1592U89) | Glaxo Wellcome | HIV infection, AIDS, ARC (RT inhibitor) |
| Acemannan | Carrington Labs (Irving, TX) | ARC |
| Acyclovir | Burroughs Wellcome | HIV infection, AIDS, ARC, in combination with AZT |
| AD-439 | Tanox Biosystems | HIV infection, AIDS, ARC |

| | | |
|---|--|---|
| AD-519 | Tanox Biosystems | HIV infection, AIDS, ARC |
| Adefovir dipivoxil AL-721 | Gilead Sciences Ethigen (Los Angeles, CA) | HIV infection ARC, PGL HIV positive, AIDS |
| Alpha Interferon | Glaxo Wellcome | Kaposi's sarcoma, HIV in combination w/Retrovir |
| Ansamycin LM 427 | Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT) | ARC |
| Antibody which neutralizes pH labile alpha aberrant Interferon AR177 | Advanced Biotherapy Concepts (Rockville, MD) | AIDS, ARC |
| beta-fluoro-ddA | Aronex Pharm | HIV infection, AIDS, ARC |
| BMS-232623 (CGP-73547) | Nat'l Cancer Institute | AIDS-associated diseases |
| BMS-234475 (CGP-61755) | Bristol-Myers Squibb/ Novartis | HIV infection, AIDS, ARC (protease inhibitor) |
| (-) 6-Chloro-4(S)- cyclopropylethynyl- 4(S)-trifluoro- methyl-1,4-dihydro- 2H-3,1-benzoxazin- 2-one CI-1012 | Merck Warner-Lambert | HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor) HIV-1 infection |

| | | |
|-----------------|--|--|
| Cidofovir | Gilead Science | CMV retinitis, herpes, papillomavirus |
| Curdlan sulfate | AJI Pharma USA | HIV infection |
| Cytomegalovirus | MedImmune | CMV retinitis |
| immune globin | | |
| Cytovene | Syntex | sight threatening |
| Ganciclovir | | CMV peripheral CMV retinitis |
| Delaviridine | Pharmacia-Upjohn | HIV infection, AIDS, ARC (RT inhibitor) |
| Dextran Sulfate | Ueno Fine Chem. Ind. Ltd. (Osaka, Japan) | AIDS, ARC, HIV positive asymptomatic |
| ddC | Hoffman-La Roche | HIV infection, AIDS, ARC |
| Dideoxycytidine | | |
| ddI | Bristol-Myers Squibb | HIV infection, AIDS, ARC; combination with AZT/d4T |
| Dideoxyinosine | | |
| DMP-266 | DuPont-Merck Pharmaceuticals | HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor) |
| DMP-450 | AVID (Camden, NJ) | HIV infection, AIDS, ARC (protease inhibitor) |
| Efavirenz | DuPont Merck | HIV infection, AIDS, ARC (non-nucleoside RT inhibitor) |
| (DMP 266) | | |

| | | |
|--------------------------------------|-------------------------------------|---|
| EL10 | Elan Corp, PLC (Gainesville, GA) | HIV infection |
| Famciclovir | Smith Kline | herpes zoster, herpes simplex |
| FTC | Emory University | HIV infection, AIDS, ARC (reverse transcriptase inhibitor) |
| GS 840 | Gilead | HIV infection, AIDS, ARC (reverse transcriptase inhibitor) |
| GW 141 | Glaxo Welcome | HIV infection, AIDS, ARC (protease inhibitor) |
| GW 1592 | Glaxo Welcome | HIV infection, AIDS, ARC (reverse transcriptase inhibitor) |
| HBV097 | Hoechst Marion Roussel | HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor) |
| Hypericin | VIMRx Pharm. | HIV infection, AIDS, ARC |
| Recombinant Human Interferon Beta | Triton Biosciences (Alameda, CA) | AIDS, Kaposi's sarcoma, ARC |
| Interferon alfa-n3 | Interferon Sciences | ARC, AIDS |
| Indinavir | Merck | HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC |

| | | |
|-------------------------------|-------------------------------------|--|
| ISIS 2922 | ISIS Pharmaceuticals | CMV retinitis |
| KN1-272 | Nat'l Cancer Institute | HIV-assoc. diseases |
| Lamivudine, 3TC | Glaxo Wellcome | HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT |
| Lobucavir | Bristol-Myers Squibb | CMV infection |
| Nelfinavir | Agouron Pharmaceuticals | HIV infection, AIDS, ARC (protease inhibitor) |
| Nevirapine | Boeheringer Ingleheim | HIV infection, AIDS, ARC (RT inhibitor) |
| Novapren | Novaferon Labs, Inc. (Akron, OH) | HIV inhibitor |
| Peptide T | Peninsula Labs | AIDS |
| Octapeptide Sequence | (Belmont, CA) | |
| Trisodium Phosphonoformate | Astra Pharm. Products, Inc | CMV retinitis, HIV infection, other CMV infections |
| PNU-140690 | Pharmacia Upjohn | HIV infection, AIDS, ARC (protease inhibitor) |
| Probucol | Vyrex | HIV infection, AIDS |
| RBC-CD4 | Sheffield Med. Tech (Houston TX) | HIV infection, AIDS, ARC |
| Ritonavir | Abbott | HIV infection, AIDS, ARC (protease inhibitor) |

| | | |
|--|---|---|
| Saquinavir | Hoffmann-LaRoche | HIV infection, AIDS, ARC (protease inhibitor) |
| Stavudine; d4T Dididehydrodeoxy-thymidine | Bristol-Myers Squibb | HIV infection, AIDS, ARC |
| Valaciclovir | Glaxo Wellcome | genital HSV & CMV infections |
| Virazole Ribavirin VX-478 | Viratek/ICN (Costa Mesa, CA) Vertex | asymptomatic HIV positive, LAS, ARC HIV infection, AIDS, ARC |
| Zalcitabine | Hoffmann-La Roche | HIV infection, AIDS, ARC, with AZT |
| Zidovudine; AZT | Glaxo Wellcome | HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies |

IMMUNO-MODULATORS

| <u>Drug Name</u> | <u>Manufacturer</u> | <u>Indication</u> |
|------------------|---------------------------------------|-----------------------------------|
| AS-101 | Wyeth-Ayerst | AIDS |
| Bropirimine | Pharmacia Upjohn | advanced AIDS |
| Acemannan | Carrington Labs, Inc. (Irving, TX) | AIDS, ARC |
| CL246,738 | American Cyanamid Lederle Labs | AIDS, Kaposi's sarcoma |
| EL10 | Elan Corp, PLC (Gainesville, GA) | HIV infection |
| FP-21399 | Fuki ImmunoPharm | blocks HIV fusion with CD4+ cells |

| | | |
|---|-------------------------------------|---|
| Gamma Interferon | Genentech | ARC, in combination w/TNF (tumor necrosis factor) |
| Granulocyte Macrophage Colony Stimulating Factor | Genetics Institute Sandoz | AIDS |
| Granulocyte Macrophage Colony Stimulating Factor | Hoeschst-Roussel Immunex | AIDS |
| Granulocyte Macrophage Colony Stimulating Factor | Schering-Plough | AIDS, combination w/AZT |
| HIV Core Particle Immunostimulant | Rorer | seropositive HIV |
| IL-2 | Cetus | AIDS, in combination w/AZT |
| Interleukin-2 | Hoffman-La Roche | AIDS, ARC, HIV, in combination w/AZT |
| IL-2 | Immunex | AIDS, increase in CD4 cell counts |
| IL-2 | Chiron | |
| Interleukin-2 (aldeslukin) | | |
| Immune Globulin Intravenous (human) | Cutter Biological (Berkeley, CA) | pediatric AIDS, in combination w/AZT |
| IMREG-1 | Imreg (New Orleans, LA) | AIDS, Kaposi's sarcoma, ARC, PGL |
| IMREG-2 | Imreg (New Orleans, LA) | AIDS, Kaposi's sarcoma, ARC, PGL |
| Imuthiol Diethyl Dithio Carbamate | Merieux Institute | AIDS, ARC |
| Alpha-2 Interferon | Schering Plough | Kaposi's sarcoma w/AZT, AIDS |

| | | |
|---------------------------|--|------------------------------------|
| Methionine- Enkephalin | TNI Pharmaceutical (Chicago, IL) | AIDS, ARC |
| MTP-PE | Ciba-Geigy Corp. | Kaposi's sarcoma |
| Muramyl-Tripeptide | | |
| Granulocyte | Amgen | AIDS, in combination |
| Colony Stimulating | | w/AZT |
| Factor | | |
| Remune | Immune Response Corp. | immunotherapeutic |
| rCD4 | Genentech | AIDS, ARC |
| Recombinant | | |
| Soluble Human CD4 | | |
| rCD4-IgG | | AIDS, ARC |
| hybrids | | |
| Recombinant | Biogen | AIDS, ARC |
| Soluble Human CD4 | | |
| Interferon | Hoffman-La Roche | Kaposi's sarcoma |
| Alfa 2a | | AIDS, ARC, in combination w/AZT |
| SK&F106528 | Smith Kline | HIV infection |
| Soluble T4 | | |
| Thymopentin | Immunobiology Research Institute (Annandale, NJ) | HIV infection |
| Tumor Necrosis | Genentech | ARC, in combination |
| Factor; TNF | | w/gamma Interferon |

ANTI-INFECTIVES

| <u>Drug Name</u> | <u>Manufacturer</u> | <u>Indication</u> |
|--------------------------------|---------------------|-------------------|
| Clindamycin with Primaquine | Pharmacia Upjohn | PCP |

| | | |
|-------------------------------|--------------------|--|
| Fluconazole | Pfizer | cryptococcal meningitis, candidiasis |
| Pastille | Squibb Corp. | prevention of |
| Nystatin Pastille | | oral candidiasis |
| Ornidyl | Merrell Dow | PCP |
| Eflornithine | | |
| Pentamidine | LyphoMed | PCP treatment |
| Isethionate (IM & IV) | (Rosemont, IL) | |
| Trimethoprim | | antibacterial |
| Trimethoprim/sulfa | | antibacterial |
| Piritrexim | Burroughs Wellcome | PCP treatment |
| Pentamidine | Fisons Corporation | PCP prophylaxis |
| isethionate for inhalation | | |
| Spiramycin | Rhone-Poulenc | cryptosporidial diarrhea |
| Intraconazole- | Janssen Pharm. | histoplasmosis; |
| R51211 | | cryptococcal meningitis |
| Trimetrexate | Warner-Lambert | PCP |

OTHER

| <u>Drug Name</u> | <u>Manufacturer</u> | <u>Indication</u> |
|-------------------|---------------------|----------------------------|
| Daunorubicin | NeXstar, Sequus | Karposi's sarcoma |
| Recombinant Human | Ortho Pharm. Corp. | severe anemia |
| Erythropoietin | | assoc. with AZT therapy |
| Recombinant Human | Serono | AIDS-related wasting, |
| Growth Hormone | | cachexia |

| | | |
|-------------------|----------------------|---|
| Megestrol Acetate | Bristol-Myers Squibb | treatment of anorexia assoc. w/AIDS |
| Testosterone | Alza, Smith Kline | AIDS-related wasting |
| Total Enteral | Norwich Eaton | diarrhea and |
| Nutrition | Pharmaceuticals | malabsorption related to AIDS |

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments of with a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4)

zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and lamivudine.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

5 Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide
10 pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium
15 phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the
20 gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control
25 release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed
30 with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example
35 sodium carboxymethylcellulose, methylcellulose, hydroxy-

propylmethylcellulose, sodium alginate, polyvinyl- pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example

5 polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as

10 polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as

15 sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax,

20 hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation

25 of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening,

30 flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying

35 agents may be naturally- occurring gums, for example gum acacia or

gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example
5 polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and
10 flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been
15 mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition,
20 sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be
25 administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene
30 glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of The present invention are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

5 In the treatment or prevention of conditions which require chemokine receptor modulation an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably
10 about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0
15 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per
20 day, preferably once or twice per day.

 It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that
25 compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

 Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples.

30 The compounds of the present invention are prepared by alkylating azacycle I, in which $R_1 = H$, under appropriate conditions (Scheme 1). The required azacycle starting materials are prepared using methods described in the literature; more specifically, as described in Claremon, D.A. *et al*, European Patent 0 431 943 943 A2,
35 Evans, B.E. *et al*, U.S. Patent 5,091,387, Davis, L. *et al*, U.S. Patent

4,420,485, all of which are incorporated by reference, and Parham *et al*, Journal of Organic Chemistry, 41, 2628 (1976).

Thus, azacycle I ($R_1=H$) is combined with the appropriate aldehyde and the intermediate imine is reduced to the tertiary amine
5 chemically (e.g. using sodium cyanoborohydride) or catalytically (e.g. using hydrogen and palladium on carbon or Raney nickel catalyst) (Scheme 1). The aldehyde needed for this reaction can be prepared by methods generally known in the chemical literature; for the purposes of the present invention the preparation of a representative aldehyde is
10 described in Hale, J.J.; Finke, P.E.; MacCoss, M. Bioorganic and Medicinal Chemistry Letters, 2, (Feb. 1993).

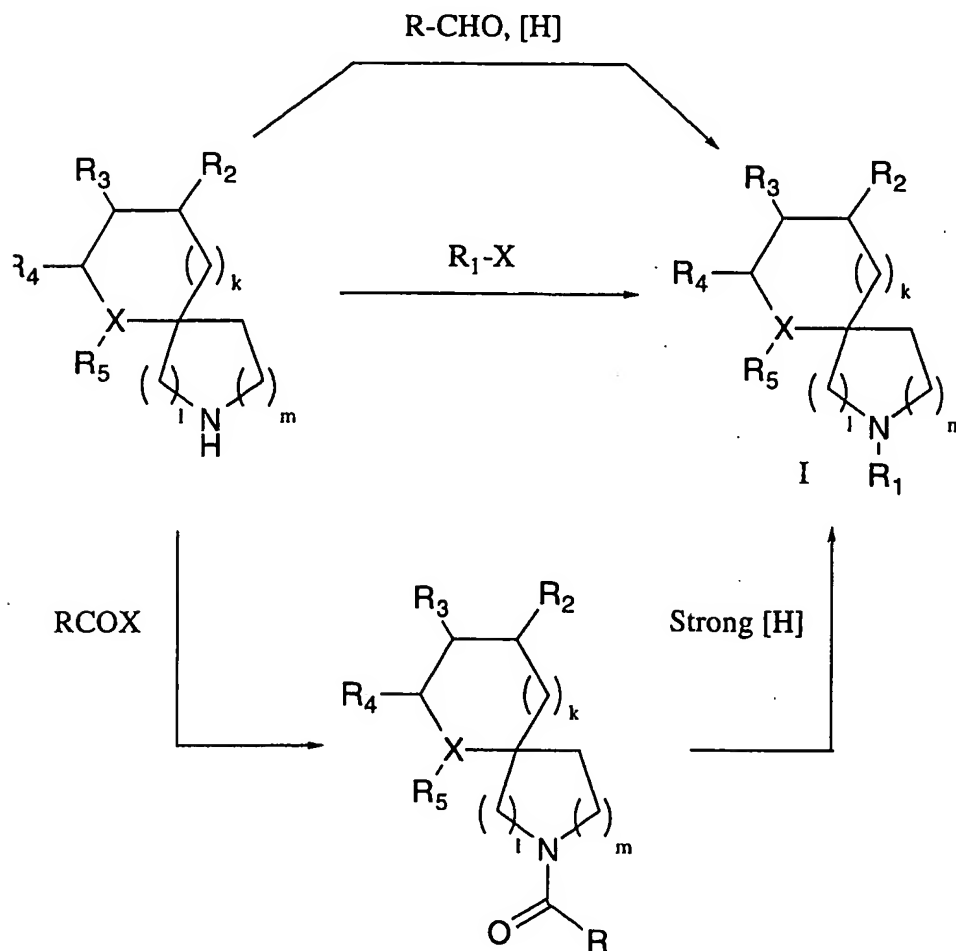
In an alternative embodiment of the present invention, azacycle I ($R_1=H$) can be alkylated with an alkyl halide or alkyl sulfonate ester (with or without an added base to neutralize the mineral acid or
15 sulfonic acid by-product) to give the desired compound (Scheme 1). The alkyl halide or alkyl sulfonate needed for this reaction can be prepared by methods generally known in the chemical literature; for the purposes of the present invention an aldehyde, prepared as described above, can be reduced to an alcohol with sodium borohydride, diisobutylaluminum
20 hydride or lithium aluminum hydride, and the product alcohol converted to either the alkyl halide using methods described in March J. "Advanced Organic Chemistry", 3rd ed., John Wiley & Sons, New York, pp. 382-384 (1985), or alkyl sulfonate ester using methods described in March J. "Advanced Organic Chemistry", 3rd ed., John Wiley & Sons,
25 New York, p. 444 (1985).

In an alternative embodiment of the present invention, I ($R_1 = H$) can be acylated to give the tertiary amide and subsequent reduction with a strong reducing agent (e.g. diborane including borane dimethylsulfide; and, lithium aluminum hydride) will give the desired
30 compound (Scheme 1). The acylating agent needed for this reaction can be prepared by methods generally known in the chemical literature; for the purposes of the present invention an aldehyde, prepared as described above, can be oxidized using such commonly used reagents as permanganate in acid or silver oxide, and the resulting acid activated as
35 an acid chloride or mixed anhydride which can be used to acylate I ($R_1 =$

H). The product amide can be reduced with a strong reducing agent, such as diborane or lithium aluminum hydride, to give the tertiary amine.

Scheme 1

5



wherein R_1 as defined in this specification is R-CH_2 .

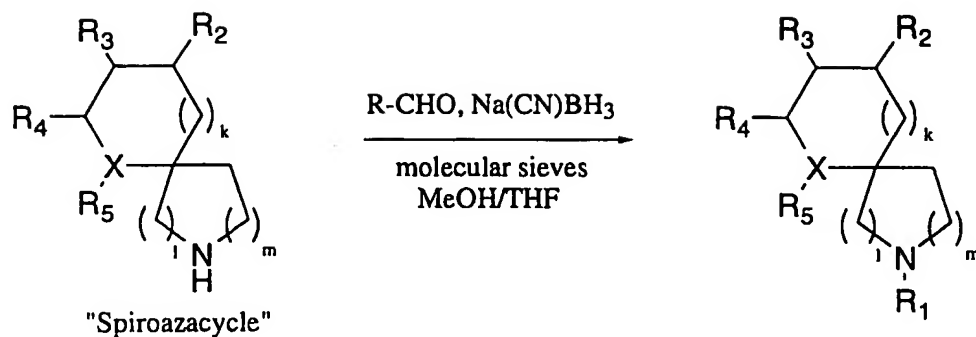
The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 1

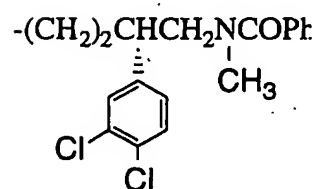
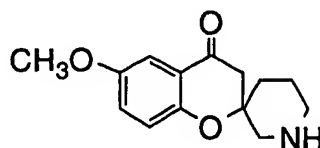
1'-(3-(S)-(3,4-Dichlorophenyl)-4-(N-methyl)benzamido)butyl)spiro(1H-indene-1,4'-piperidine)

5 A mixture of 125 mg (0.36 mmol) of (3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido)butanal, 107 mg (0.48 mmol) of spiro(1H-indene-1,4'-piperidine) hydrochloride, and 100 mg of activated 3 Å molecular sieves in 2 mL of methanol was treated with 1.5 mL of 1.0 M sodium cyanoborohydride solution in THF and stirred at room temperature for
10 20 hours. The mixture was filtered through a pad of Celite; the reaction flask and filtered solids were rinsed well with methanol (~25 mL). Saturated sodium bicarbonate solution (5 mL) was added to the filtrate and the resulting milky mixture was concentrated *in vacuo*. The
15 residue was partitioned between 25 mL of ethyl acetate and 10 mL of water and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. Flash chromatography on 8 g of silica gel using ether, then 20:1 v/v ether/methanol as the eluant afforded 146 mg (78%) of the title compound as a foam. ¹H NMR (CDCl₃, 400 MHz, ppm, ranges are given due to amide rotamers and line
20 broadening): δ 0.80-4.05 ppm (18 H), 6.75 (app s, 1 H), 6.79 (app s, 1 H), 6.95-7.50 (12 H). 2.69 and 3.04 (-CH₂N(CH₃)COPh). Mass Spectrum (FAB): 521 (M+H, ³⁷Cl + ³⁵Cl isotope), 519 (M+H, ³⁵Cl + ³⁵Cl isotope).

25 The following table summarizes compounds that were prepared using a procedure analogous to Example 1 substituting the required spiroazacycle hydrochloride for the spiro(1H-indene-1,4'-piperidine) hydrochloride. Methylene chloride/methanol/ ammonium hydroxide (40:1:0.1 v/v/v) was used as the chromatography eluant.

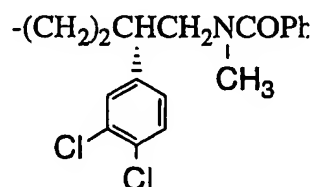
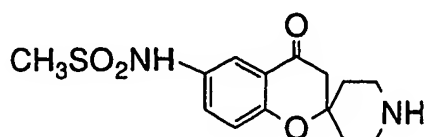
EXAMPLE"Spiroazacycle"R₁

2



¹H NMR (CDCl₃, 400 MHz, ppm): δ 1.50-3.75 (20 H), 3.77 (s, 3 H), 6.62-7.43 (11 H). Mass Spectrum (FAB): 583 (M+H, ³⁷Cl + ³⁵Cl isotope), 581 (M+H, ³⁵Cl + ³⁵Cl isotope).

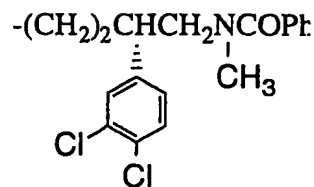
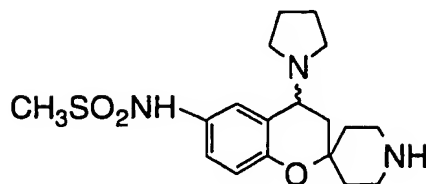
3



¹H NMR (CDCl₃, 400 MHz, ppm): δ 1.58-3.95 (24 H), 6.72-7.62 (11 H). Mass Spectrum (FAB): 646 (M+H, ³⁷Cl + ³⁵Cl isotope), 644 (M+H, ³⁵Cl + ³⁵Cl isotope).

EXAMPLE"Spiroazacycle"R₁

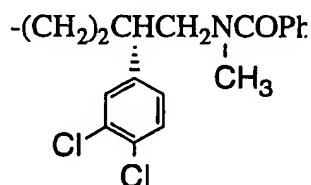
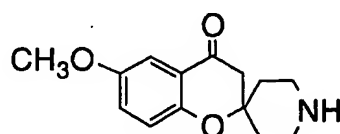
4


¹H NMR (CDCl₃, 400 MHz, ppm): δ 1.70-4.18 (33 H), 6.72-7.47 (11 H).

 Mass Spectrum (FAB): 701 (M+H, ³⁷Cl + ³⁵Cl isotope), 699 (M+H, ³⁵Cl + ³⁵Cl isotope).

5

5

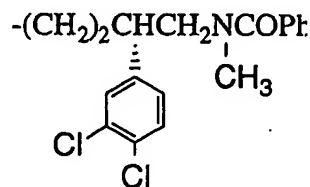
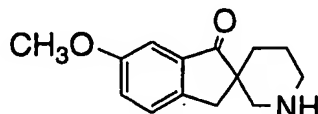

¹H NMR (CDCl₃, 400 MHz, ppm): δ 1.56-3.57 (20 H), 3.90 (m, 1 H), 6.72-7.43 (11 H), 3.77 (CH₃O-) Mass Spectrum (FAB): 583 (M+H, ³⁷Cl + ³⁵Cl

 isotope), 581 (M+H, ³⁵Cl + ³⁵Cl isotope).

10

EXAMPLE"Spiroazacycle"R₁

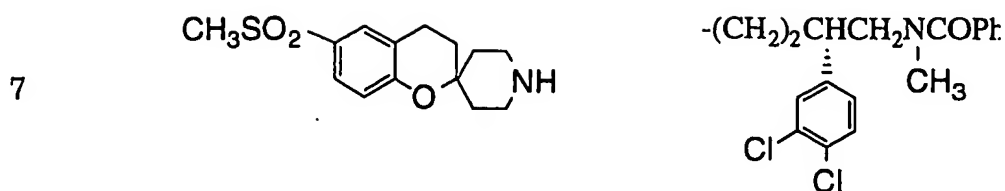
6


¹H NMR (CDCl₃, 400 MHz, ppm): δ 1.39-3.50 (20 H), 6.70-7.40 (11 H).

 3.80 (CH₃O-) Mass Spectrum (FAB): 567 (M+H, ³⁷Cl + ³⁵Cl isotope), 565

 (M+H, ³⁵Cl + ³⁵Cl isotope).

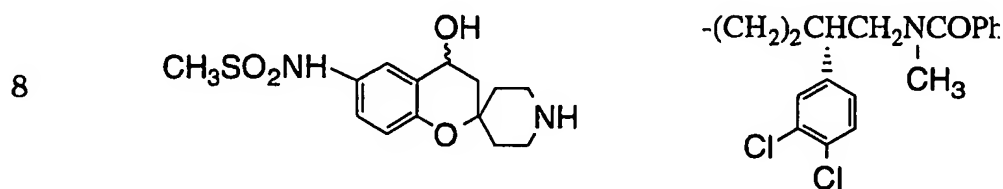
15



1H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.45-3.97 (25 H), 6.73-7.65 (11 H).

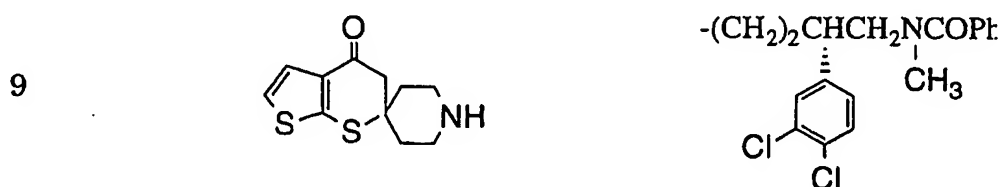
Mass Spectrum (FAB): 617 ($M+H$, $^{37}Cl + ^{35}Cl$ isotope), 615 ($M+H$, $^{35}Cl + ^{35}Cl$ isotope).

5

EXAMPLE"Spiroazacycle"R₁

1H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.65-3.60 (24 H), 3.95 (m, 1 H), 4.75 (m, 1 H), 6.70-7.40 (11 H). Mass Spectrum (FAB): 648 ($M+H$, $^{37}Cl + ^{35}Cl$ isotope), 646 ($M+H$, $^{35}Cl + ^{35}Cl$ isotope).

10

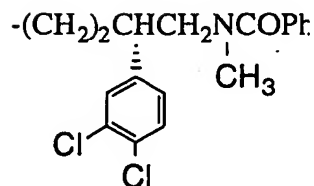
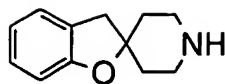


1H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.40-3.95 (16 H), 6.70-7.45 (8 H), 7.00 (app s, 1 H), 7.03 (app s, 1 H), 2.67 and 2.81 ($-CH_2N(CH_3)COPh$) Mass Spectrum (FAB): 575 ($M+H$, $^{37}Cl + ^{35}Cl$ isotope), 573 ($M+H$, $^{35}Cl + ^{35}Cl$ isotope).

15

EXAMPLE"Spiroazacycle"R₁

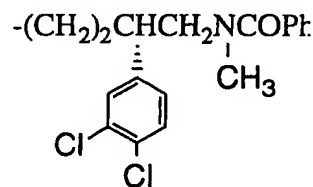
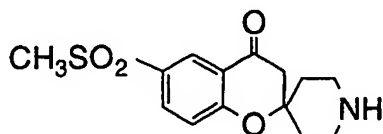
10



^1H NMR (CDCl_3 , 400 MHz, ppm): δ 1.45-3.95 (17 H), 6.70-7.45 (12 H) 2.69 and 2.97 ($-\text{CH}_2\text{N}(\text{CH}_3)\text{COPh}$)

Mass Spectrum (FAB): 525 ($\text{M}+\text{H}$, ^{37}Cl + ^{35}Cl isotope), 523 ($\text{M}+\text{H}$, ^{35}Cl + ^{35}Cl isotope).

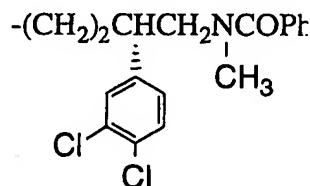
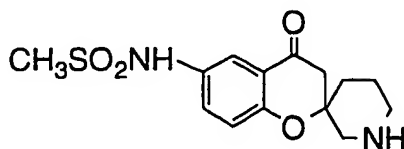
11



^1H NMR (CDCl_3 , 400 MHz, ppm): δ 1.60-3.95 (23 H), 6.70-7.42 (9 H), 7.98 (dd, 1 H, $J = 2.4, 8.7$), 8.41 (d, 1 H, $J = 2.32$). Mass Spectrum (FAB): 631 ($\text{M}+\text{H}$, ^{37}Cl + ^{35}Cl isotope), 629 ($\text{M}+\text{H}$, ^{35}Cl + ^{35}Cl isotope).

EXAMPLE"Spiroazacycle"R1

12



^1H NMR (CDCl_3 , 400 MHz, ppm): δ 1.15-4.00 (24 H), 6.65-7.77 (11 H).
Mass Spectrum (FAB): 645 ($\text{M}+\text{H}$, ^{37}Cl + ^{35}Cl isotope), 643 ($\text{M}+\text{H}$, ^{35}Cl + ^{35}Cl isotope).

EXAMPLE 13

1'-3-(S)-(3,4-Dichlorophenyl)-4-((N-methyl)-3,5-bis(trifluoromethyl)-
5 benzamidoethyl)spiro(1H-indene-1,4'-piperidine)

STEP 1: N-Methyl-N-((2S)-(3,4-dichlorophenyl)-4-pentenyl)-3,5-bis(trifluoromethyl) benzamide.

A rapidly stirred mixture of 135 mg (0.55 mmol) of N-methyl
10 (2S)-(3,4-dichlorophenyl)-4-pentenamine, 2 mL of saturated aqueous sodium bicarbonate solution and 4 mL of toluene was treated with 0.35 mL (1.9 mmol) of 3,5-bis(trifluoromethyl) benzoyl chloride and the resulting mixture was stirred at room temperature for 20 minutes. The reaction mixture was diluted with 25 mL of ether and the layers were
15 separated. The organic layer was washed with 10 mL of 2.0 N sodium hydroxide solution, 10 mL of 2.0 N hydrochloric acid solution, 10 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated *in vacuo*. Flash chromatography on 12 g of silica gel using 4:1 v/v hexanes/ether as the eluant afforded 263 mg (99%)
20 of the title compound as an oil, $[\alpha]_D = -27.6$ ($c = 0.5$, CHCl_3 , 20 °C). ^1H NMR (CDCl_3 , 400 MHz, ppm, ranges are given due to amide rotamers and line broadening): δ 2.15-3.85 (5 H), 2.71 and 3.07 (3 H, - $\text{CH}_2\text{N}(\text{CH}_3)\text{COAr}$), 4.95-5.07 (2 H, - $\text{CH}_2\text{CH}=\text{CH}_2$), 5.40-5.75 (1 H, - $\text{CH}_2\text{CH}=\text{CH}_2$), 6.70-8.50 (6 H).
25 IR (neat): 1726, 1643, 1470, 1371, 1228, 1122, 993, 905, 681.
Mass Spectrum (FAB): 486 ($^{37}\text{Cl} + ^{35}\text{Cl}$ isotope), 484 ($^{35}\text{Cl} + ^{35}\text{Cl}$ isotope).

Analysis: Calculated for $\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{F}_6\text{NO}$
C, 52.08; H, 3.54; N, 2.89
30 Found: C, 51.13; H, 3.31; N, 2.45.

STEP 2: 1'-3-(S)-(3,4-Dichlorophenyl)-4-((N-methyl)-3,5-bis(trifluoromethyl) benzamidoethyl)spiro(1H-indene-1,4'-piperidine).

A solution of 250 mg (0.52 mmol) of N-methyl-N-((2S)-(3,4-dichlorophenyl)-4-pentenyl)-3,5-bis(trifluoromethyl) benzamide
35

(EXAMPLE 13, STEP 1) in 8 mL of 2:1:1 v/v/v acetone/ *t*-butanol/water was treated with 5 mg (0.02 mmol) of osmium tetroxide. After 5 min, 91 mg (0.77 mmol) of *N*-methyilmorpholine *N*-oxide was added and the resulting mixture was stirred at room temperature for 1.5 h. The
5 reaction was quenched with approximately 100 mg of sodium bisulfite and concentrated *in vacuo* to 25% of the original volume. The residue was partitioned between 50 mL of methylene chloride and 20 mL of water and the layers were separated. The organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 25 mL of
10 methylene chloride; the extract was dried and combined with the original organic layer. The combined organic layers were concentrated *in vacuo* to afford the crude diol.

A solution of the diol in 8 mL of 3:1 v/v THF/water was treated with 197 mg (0.92 mmol) of sodium periodate. After 30 min, the
15 reaction mixture was partitioned between 50 mL of ether and 25 mL of water and the layers were separated. The organic layer was dried. The aqueous layer was extracted with 50 mL of ether; the extract was dried and combined with the original organic layer. The combined organic layers were concentrated *in vacuo*. The residue was filtered through a
20 pad of 10 g of silica gel using 3:2 v/v ether/hexanes as the eluant to afford 154 mg (61%) of aldehyde.

A solution of 150 mg (0.31 mmol) of aldehyde and 115 mg (0.52 mmol) of spiro(1*H*-indene-1,4'-piperidine) hydrochloride in 3 mL of methanol was treated with 1.5 mL of 1 M sodium cyanoborohydride
25 solution in THF. The mixture was stirred at rt for 16 h. The reaction was quenched with 5 mL of sat'd NaHCO₃ and the resulting mixture was partitioned between 30 mL of ether and 10 mL of water and the layers were separated. The organic layer was dried. The aqueous layer was extracted with 30 mL of ether; the extract was dried and combined
30 with the original organic layer. The combined organic layers were concentrated *in vacuo*. Flash chromatography on 10 g of silica gel using 100:1 v/v, then 40:1 v/v CH₂Cl₂/methanol as the eluant afforded 134 mg (66% from the intermediate aldehyde) of the title compound as a foam.

¹H NMR (CDCl₃, 400 MHz, ppm, ranges are given due to amide rotamers and line broadening): δ 1.30-3.90 (15 H), 6.73-6.80 (m, 2 H), 7.05-7.90 (10 H). 2.72 and 3.12 (-CH₂N(CH₃)COAr)

Mass Spectrum (FAB): 656 (³⁷Cl + ³⁵Cl isotope), 654 (³⁵Cl + ³⁵Cl isotope).

Analysis: Calculated for C₃₃H₃₀Cl₂F₆N₂O

C, 60.47; H, 4.61; N, 4.27

Found: C, 59.84; H, 4.46; N, 3.97.

10

EXAMPLE 14

1'-((3S)-(3,4-Dichlorophenyl)-4-(N-methyl)benzamido-butyl)-3,4-dihydro-4-hydroxy-6-methoxy-spiro[2H-1-benzopyran-2,3'-piperidine]

15 A solution of 51 mg (0.088 mmol) of 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)-3,4-dihydro-4-oxo-6-methoxy-spiro[2H-1-benzopyran-2,3'-piperidine] (EXAMPLE 2) in 1 mL of methanol at 0 °C was treated with 10 mg of sodium borohydride. The resulting mixture was warmed to room temperature and stirred for 30 minutes. The reaction was quenched with 1.0 mL of 2.0 N sodium hydroxide solution and extracted with 3 x 10 mL of methylene chloride. The organic extracts were combined, dried over sodium sulfate and concentrated to afford 53 mg of the title compound. ¹H NMR (CDCl₃, 400 MHz, ppm, ranges are given due to amide rotamers and line broadening): δ 1.40-5.00 (25 H), 6.70-7.42 (11 H). Mass Spectrum (FAB): 25 585 (³⁷Cl + ³⁵Cl isotope), 583 (³⁵Cl + ³⁵Cl isotope).

EXAMPLE 15

30 1'-((3S)-(3,4-Dichlorophenyl)-4-(N-methyl)benzamido-butyl)-3,4-dihydro-4-hydroxy-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperidine]

The title compound was obtained from 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)-3,4-dihydro-4-oxo-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperidine] (EXAMPLE 5) using a procedure analogous to EXAMPLE 14.

¹H NMR (CDCl₃, 400 MHz, ppm, ranges are given due to amide rotamers and line broadening): δ 1.40-3.58 (20 H), 3.86 (m, 1 H), 4.479 (br s, 1 H), 6.70-7.41 (11 H). 3.75 (3 H, CH₃O-) Mass Spectrum (FAB): 585 (³⁷Cl + ³⁵Cl isotope), 583 (³⁵Cl + ³⁵Cl isotope).

5

EXAMPLE 16

1'-((3S)-(3,4-Dichlorophenyl)-4-(N-methyl)benzamido-butyl)spiro-(indane-1,4'-piperidine)

10

A mixture of 50 mg (0.096 mmol) of 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)spiro(1H-indene-1,4'-piperidine) (EXAMPLE 1) and 7.5 mg 10% palladium on carbon catalyst in 2 mL of absolute ethanol was stirred under an atmosphere of hydrogen for 5 hours. The catalyst was filtered on a pad of Celite, the flask and filtered solids rinsed well with ethanol (20 mL) and the filtrate was concentrated *in vacuo*. Flash chromatography on 4 g of silica gel afforded 43 mg of the title compound as an oil.

¹H NMR (CDCl₃, 400 MHz, ppm, ranges are given due to amide rotamers and line broadening): δ 1.45-4.05 (22 H), 6.80-7.60 (12 H). Mass Spectrum (FAB): 523 (³⁷Cl + ³⁵Cl isotope), 521 (³⁵Cl + ³⁵Cl isotope).

20

EXAMPLE 17

25

1'-(1-Oxo-(3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)-spiro(1H-indene-1,4'-piperidine)

STEP 1: (3S)-(3,4-Dichlorophenyl)-4-(N-methyl)benzamido-butanoic acid.

A solution of 525 mg (1.5 mmol) of (3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butanal in 10 mL of 1:1 v/v methanol/ 1.0 N sodium hydroxide solution was treated with 463 mg (2.0 mmol) of freshly prepared silver oxide and the resulting mixture was stirred at room temperature for 20 hours. The reaction mixture was filtered through a

30

pad of Celite and the flask and filtered solids were washed well with methanol (~25 mL). The filtrate was concentrated to ~10% of the original volume *in vacuo* and the residue was partitioned between 50 mL of ether and 50 mL of 2.0 N hydrochloric acid solution and the layers were
5 separated. The organic layer was washed with 25 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated *in vacuo*. Flash chromatography on 30 g of silica gel using 1:1 v/v ethyl acetate/hexanes + 1% acetic acid as the eluant afforded 540 mg (98%) of the title compound as a foam. ¹H NMR (CDCl₃, 400 MHz, ppm, ranges are given due to amide rotamers and line broadening): δ
10 1.20-4.00 (8 H), 6.70-7.45 (8 H). Mass Spectrum (FAB): 368 (³⁷Cl + ³⁵Cl isotope), 366 (³⁵Cl + ³⁵Cl isotope).

STEP 2: 1'-(1-Oxo-(3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-
15 butyl)spiro (1H-indene-1,4'-piperidine).

A solution of 315 mg (0.86 mmol) of (3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-
butanoic acid (EXAMPLE 17, STEP 1) in 3 mL of methylene chloride was treated with 0.5 mL of oxalyl
chloride and 1 drop of N,N-dimethylformamide. The resulting solution
20 was stirred at room temperature for 20 minutes, then concentrated *in vacuo*. The residue was twice redissolved in 10 mL of ether and concentrated *in vacuo*. A solution of the crude acid chloride in 5 mL of methylene chloride was slowly added to a solution of 300 mg (1.62 mmol)
of spiro(1H-indene-1,4'-piperidine) and 0.52 mL (3.0 mmol) of N,N-
25 diisopropylethyl amine in 5 mL of methylene chloride at 0 °C and the resulting solution was stirred cold for 1 hour. The reaction mixture was diluted with 40 mL of ethyl acetate and washed with 20 mL of 2.0 N
hydrochloric acid solution, 20 mL of saturated aqueous sodium bicarbonate solution, 20 mL of saturated sodium chloride solution, dried
30 over magnesium sulfate and concentrated *in vacuo*. Flash chromatography on 25 g of silica gel using 7:3 v/v, then 1:1 v/v methylene chloride/ethyl acetate as the eluant afforded 302 mg (66%) of the title compound as a foam. ¹H NMR (CDCl₃, 400 MHz, ppm, ranges are given due to amide rotamers and line broadening): δ 1.20-2.00 (5 H), 2.40-4.70

(11 H), 6.79 (app s, 2 H), 6.85-7.55 (12 H). Mass Spectrum (FAB): 535 (^{37}Cl + ^{35}Cl isotope), 533 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 18

5

1'-((3S)-(3,4-Dichlorophenyl)-(4)-((N-methyl)benzamido)pentyl)spiro-(1H-indene-1,4'-piperidine)

STEP 1: N-Methoxy-N-methyl-(2S)-(3,4-dichlorophenyl)-4-pentenamide.

- A mixture of 306 mg (1.25 mmol) of (2S)-(3,4-dichlorophenyl)-4-pentenoic acid and 202 mg (1.50 mmol) of 1-hydroxybenzotriazole hydrate in 10 mL of methylene chloride was cooled to 0°C and treated with 287 mg (1.50 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. The cooling bath was removed and after 45 min. a solution of 365 mg (3.75 mmol) of N,O-dimethylhydroxylamine hydrochloride and 522 μL (3.75 mmol) of triethylamine in 10 mL of methylene chloride was added via cannula. The mixture was then stirred at 22°C for 4 hours and then quenched with 10 mL of water and diluted with 8 mL of methylene chloride. The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 10 mL).
- The combined organic layers were washed with 10 mL of brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography on 75 g of silica gel using 1:9 v/v ethyl acetate/hexane as the eluant afforded 319 mg (89%) of the title compound as a clear oil.
- $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 2.40 (pentet, 1H), 2.75 (pentet, 1H), 3.13 (s, 3H), 3.52 (s, 3H), 3.99-4.01 (m, 1H), 4.96-5.05 (m, 2H), 5.63-5.70 (m, 1H), 7.15 (dd, 1H), 7.35 (d, 1H), 7.41 (d, 1H).
- Mass Spectrum (FAB): m/z 290 (M+H, ^{37}Cl + ^{35}Cl isotope, 50%), 288 (M+H, ^{37}Cl + ^{37}Cl isotope, 100%).

30

STEP 2: (3S)-(3,4-dichlorophenyl)-5-hexen-2-one.

A solution of 319 mg (1.11 mmol) of N-methoxy-N-methyl-(2S)-(3,4-dichlorophenyl)-4-pentenamide (EXAMPLE 18, STEP 1) in 10 mL of dry tetrahydrofuran was cooled to -70°C and treated with 1.0 mL

(1.40 mmol) of methyllithium and stirred between -70°C to -40°C. After 3 hours, the reaction was quenched with 5 mL of water, and diluted with 10 mL of ethyl acetate. The layers were separated and the organic layer was washed with water (3 x 10 mL). The aqueous layers were extracted with 10 mL of ethyl acetate. The combined organic layers were washed with 10 mL of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography on 44 g of silica gel using 1:3 v/v ethyl acetate/ hexane as the eluant afforded 250 mg (93%) of the title compound as a clear oil. ¹H-NMR (400 MHz, CDCl₃) δ 2.07 (s, 3 H), 2.36 (pentet, 1 H), 2.72 (pentet, 1 H), 3.64 (t, 1 H), 4.95-5.01 (m, 2 H), 5.55-5.65 (m, 1 H), 7.03 (dd, 1 H), 7.30 (d, 1 H), 7.39 (d, 1 H). Mass Spectrum (FAB): m/z 245 (M+H, ³⁷Cl + ³⁵Cl isotope, 30%), 243 (M+H, ³⁷Cl + ³⁷Cl isotope, 50%), 155 (60%), 119 (100%).

STEP 3: N-Methyl-(3S)-(3,4-dichlorophenyl)-5-hexen-2-amine.

A mixture of 102 mg (0.42 mmol) of (3S)-(3,4-dichlorophenyl)-5-hexen-2-one (EXAMPLE 18, STEP 2), 170 mg (2.52 mmol) of methylamine hydrochloride, and 234 µl (1.68 mmol) of triethylamine in 4.0 mL of methanol was treated with 16 mg (0.25 mmol) of sodium cyanoborohydride and stirred at 22°C for 20 hours. Saturated aqueous sodium bicarbonate solution (1.0 mL) was added and the resulting milky mixture was diluted with 5.0 mL of ethyl acetate and 5.0 mL of water. The layers were separated and the organic layer was washed with water (3 x 5 mL). The aqueous layers were extracted with 10 mL of ethyl acetate. The combined organic layers were washed with 10 mL of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography on 42 g of silica gel using 10:1 v/v ether/ hexane as the eluant afforded 64 mg of the higher R_f isomer (Isomer A) and 22 mg of a lower R_f isomer (Isomer B) both as yellow oils. ¹H-NMR (400 MHz, CDCl₃); Isomer A: δ 1.04 (d, 3 H), 2.29-2.35 (m, 4 H), 2.50-2.68 (m, 3 H), 4.86-4.95 (m, 2 H), 5.48-5.56 (m, 1 H), 7.01 (dd, 1 H), 7.26 (d, 1 H), 7.34 (d, 1 H); Isomer B: δ 0.86 (d, 3 H), 2.32-2.50 (m, 4 H), 2.51-2.53 (m, 1 H), 2.68-2.73 (m, 2 H), 4.88-4.98 (m, 2 H), 5.54-5.61 (m, 1 H), 6.97 (dd, 1 H), 7.22 (d, 1

H), 7.33 (d, 1 H). Mass Spectrum (Isomer A) (FAB): m/z 260 (M+H, ^{37}Cl + ^{35}Cl isotope, 70%), 258 (M+H, ^{35}Cl + ^{35}Cl isotope, 100%).

STEP 4: N-Methyl-N-((2)-((3S)-(3,4-dichlorophenyl))-5-hexenyl)benzamide.

5 A solution of 197 mg (0.76 mmol) of N-methyl (3S)-(3,4-dichlorophenyl)-5-hexen-2-amine (Isomer A) (EXAMPLE 18, STEP 3) in 7.0 mL of dry methylene chloride was cooled to -70°C and treated with 160 μl (1.14 mmol) of triethylamine and 177 μl (1.53 mmol) of benzoyl
10 chloride. The cooling bath was removed and the reaction was stirred at 22°C for 20 hours. The reaction was quenched with 3.0 mL of water and diluted with 8.0 mL of methylene chloride. The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 5 mL). The combined organic layers were washed with 10 mL of brine, dried
15 over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography on 43 g of silica gel using 1:3 v/v ethyl acetate/hexane as the eluant afforded 261 mg (95%) of the title compound as a clear oil. ^1H -NMR (400 MHz, CDCl_3 , ranges are given due to amide rotamers and line broadening) δ 1.38-5.55 (13H), 6.70-7.38 (9H). Mass
20 Spectrum (FAB): m/z 364 (M+H, ^{37}Cl + ^{35}Cl isotope, 100%), 362 (M+H, ^{35}Cl + ^{35}Cl isotope, 70%).

STEP 5: (3S)-(3,4-Dichlorophenyl)-(4)-(N-methyl)benzamidopentanal.

25 A solution of 261 mg (0.72 mmol) of N-methyl-N-((2?)-((3S)-(3,4-dichlorophenyl))-5-hexenyl)benzamide (EXAMPLE 18, STEP 4) in 4.0 mL of 2:1:1 v/v/v acetone/*t*-butanol/water was treated with 1.8 mg (0.01 mmol) of osmium tetroxide. After 5 min., 128 mg (1.08 mmol) of N-methylmorpholine N-oxide was added and the resulting mixture was stirred at 22°C for 2 hours. The reaction was quenched with 84 mg of
30 sodium bisulfite and concentrated *in vacuo* to 25% of the original volume. The residue was partitioned between 10 mL of methylene chloride and 15 mL of water and the layers were separated. The aqueous layer was extracted with methylene chloride (2 x 5 mL). The combined

organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*.

A solution of the crude diol in 6.0 mL of 3:1 v/v THF/water was treated with 194 mg (0.90 mmol) of sodium periodate. After 30 min., the reaction mixture was partitioned between 10 mL of ethyl ether and 10 mL of water and the layers were separated. The organic layer was washed with water (2 x 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was filtered through a pad of 76 g of silica gel using ethyl ether as the eluant to afford 183 mg (70%) of the title compound as an oil.

¹H-NMR (400 MHz, CDCl₃, ranges are given due to amide rotamers and line broadening) δ 1.33 (d, 3 H), 2.55 (s, 3 H), 2.81-2.89 (m, 3 H), 3.30-3.50 (m, 2 H), 4.90-5.10 (m, 1 H), 6.79-7.41 (m, 9 H), 9.50 (s, 1 H), 9.65 (s, 1 H). Mass Spectrum (FAB): m/z 366 (M+H, ³⁷Cl + ³⁵Cl isotope, 45%), 364 (M+H, ³⁷Cl + ³⁷Cl isotope, 65%), 242 (58%), 162 (100%), 136 (52%), 105 (53%).

STEP 6: 1'-((2)-((3S)-(3,4-Dichlorophenyl)-5-(N-methyl)benzamido)-pentyl) spiro(1H-indene-1,4'-piperidine).

A mixture of 70 mg (0.19 mmol) of (3S)-(3,4-dichlorophenyl)-(4)-(N-methyl)benzamido-pentanal (EXAMPLE 18, STEP 5), 62 mg (0.28 mmol) of spiro(1H-indene-1-4'-piperidine) hydrochloride in 3.0 mL of methanol was treated with 36 mg (0.58 mmol) of sodium cyanoborohydride and stirred at 22°C for 20 hours. Saturated sodium bicarbonate solution (1.0 mL) was added and the resulting milky mixture was concentrated to 50% of its original volume. The residue was partitioned between 20 mL of ethyl acetate and 10 mL of water and the layers were separated. The organic layer was washed with water (3 x 10 mL). The aqueous layers were extracted with 10 mL of ethyl acetate. The combined organic layers were washed with 10 mL of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography on 43 g of silica gel using 5:95 v/v methanol/methylene chloride as the eluant afforded 83 mg (81%) of the title compound as a white foam. ¹H-NMR (400 MHz, CDCl₃, ranges are given due to amide rotamers and line broadening) δ 1.22-5.11 (20 H), 6.68-

7.42 (m, 15 H). Mass Spectrum (FAB): m/z 569 (M+H, ^{37}Cl + ^{35}Cl isotope, 70%), 567 (M+H, ^{35}Cl + ^{35}Cl isotope, 100%).

EXAMPLE 19

5

1'-((2)-((3S)-(3,4-Dichlorophenyl)-5-(N-methyl)benzamido)pentyl) spiro(1H-indene-1,4'-piperidine)

The title compound was prepared from 1'-((2)-((3S)-(3,4-dichlorophenyl)-5-(N-methyl)benzamido)pentyl) spiro(1H-indene-1,4'-piperidine) (EXAMPLE 18) using a procedure identical to EXAMPLE 16. $^1\text{H-NMR}$ (400 MHz, CDCl_3 , ranges are given due to amide rotamers and line broadening) δ 1.36-5.28 (24 H), 6.77 (d, 2 H), 7.04-7.40 (m, 13 H). Mass Spectrum (FAB): m/z 538 (M+H, ^{37}Cl + ^{35}Cl isotope, 70%), 536 (M+H, ^{35}Cl + ^{35}Cl isotope, 100%).

15

EXAMPLE 20

1'-((3S)-(3,4-Dichlorophenyl)-(4)-((N-methyl)benzamido)octyl)spiro-(1H-indene-1,4'-piperidine)

The title compound was prepared in 6 steps from (2S)-(3,4-dichlorophenyl)-4-pentenoic acid using procedures identical to those in EXAMPLE 18, substituting butyllithium for methyllithium in EXAMPLE 18, STEP 2. $^1\text{H-NMR}$ (400 MHz, CDCl_3 , ranges are given due to amide rotamers and line broadening) δ 0.92 (t, 3 H), 1.20-3.00 (24 H), 6.69-6.90 (m, 4 H), 7.15-7.41 (m, 10 H). Mass Spectrum (FAB): m/z 578 (M+H, ^{37}Cl + ^{35}Cl isotope, 70%), 576 (M+H, ^{35}Cl + ^{35}Cl isotope, 100%).

25

EXAMPLE 21

1'-((4)-((3S)-(3,4-Dichlorophenyl)-1-(N-methyl)benzamido)octyl)spiro(1H-indene-1,4'-piperidine)

30

The title compound was prepared from 1'-((4)-((3S)-(3,4-dichlorophenyl)-1-(N-methyl)benzamido)octyl)spiro(1H-indene-1,4'-piperidine) (EXAMPLE 20) using a procedure identical to EXAMPLE 16.

¹H-NMR (400 MHz, CDCl₃, ranges are given due to amide rotamers and line broadening) δ 0.92 (t, 3 H), 1.35-2.87 (27 H), 6.75 (d, 2 H), 7.12-7.40 (m, 10 H). Mass Spectrum (FAB): m/z 580 (M+H, ³⁷Cl + ³⁵Cl isotope, 70%), 578 (M+H, ³⁵Cl + ³⁵Cl isotope, 100%).

5

Employing standard acylation procedures on 1'-[3-((S)-(3,4-dichlorophenyl))-4-(methylamino)butyl]-spiro[1H-indene-1,4'-piperidine (for example, as in Example 13, Step 1, or Example 18, Step 1), the following compounds were prepared:

10

EXAMPLE 22

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)thiophene-2-carboxamido-butyl)spiro[1H-indene-1,4'-piperidine]

15

Mass Spectrum (FAB) : m/Z 140,197,227,229,383,525

EXAMPLE 23

20 1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)benzenesulfonamidobutyl)spiro[1H-indene-1,4'-piperidine]

Mass Spectrum (FAB): m/Z 140,197,227,229,383,555,557

25

EXAMPLE 24

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)furan-2-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine]

30 Mass Spectrum (FAB): m/Z 140,197,227,229,383,509,511

EXAMPLE 25

35 1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)phenoxy-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine]

Mass spectrum (FAB): m/Z 140,197,227,229,383,535,538

40

EXAMPLE 26

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)phenylaminocarboxamido
butyl)spiro[1H-indene-1,4'-piperidine]

Mass Spectrum (FAB): m/Z 140,197,227,229,383,534,536

5

EXAMPLE 27

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)pyridine-2-
carboxamidobutyl)spiro[1H-indene-1,4'-piperidine]

10

Mass Spectrum (FAB): m/Z 140,197,227,229,383,520,522

EXAMPLE 28

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)pyridine-3-
carboxamidobutyl)spiro[1H-indene-1,4'-piperidine]

15

Mass Spectrum (FAB): m/Z 140,197,227,229,383,520,522

20

EXAMPLE 29

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)pyridine-4-
carboxamidobutyl)spiro[1H-indene-1,4'-piperidine]

25

Mass Spectrum (FAB): m/Z 140,197,227,229,383,520,522

EXAMPLE 30

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)benzothiophene-2-
carboxamidobutyl)spiro[1H-indene-1,4'-piperidine]

30

Mass Spectrum (FAB): m/Z 197,227,229,383,575,577

35

EXAMPLE 31

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)thiophene-2-
acetamidobutyl)spiro[1H-indene-1,4'-piperidine]

40

Mass Spectrum (FAB): m/Z 141,197,227,229,383,539,541

EXAMPLE 32

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)thiophene-3-
carboxamidobutyl)spiro[1H-indene-1,4'-piperidine]

45

Mass Spectrum (FAB): m/Z 141,197,227,229,383,525,526

EXAMPLE 33

5

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)-(3-methylthiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine]

10

Mass Spectrum (FAB): m/Z 197,227,229,383,539,541

EXAMPLE 34

15

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)-(5-methylthiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine]

Mass Spectrum (FAB): m/Z 141,197,227,229,383,539,541

EXAMPLE 35

20

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)-(5-chlorothiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine]

Mass Spectrum (FAB): m/Z 197,227,229,383,559,561 (cluster)

25

EXAMPLE 36

30

1'-((3S)-(3,4-Dichlorophenyl)-4-((N-methyl)-(2,3-dibromothiophene-5-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine]

Mass Spectrum (FAB): m/Z 140,197,227,229,383,682 (cluster)

EXAMPLE 37

35

3-(S)-(3,4-Dichlorophenyl)-4-((t-butoxycarbonyl)methylamino)butanal.

40 A solution of 10 g (41 mmol) of 3-(S)-(3,4-dichlorophenyl)-4-methylamino-1-pentene in 100 mL of CH₂Cl₂ was cooled in ice bath and treated with 5.8 mL (41 mmol) of triethylamine (Et₃N) and 9 g (41 mmol) of di-t-butyl dicarbonate. The cold bath was removed after 5 min and the stirring was continued for 1 h. The reaction mixture was diluted with CH₂Cl₂ and washed with water, 1.2 N HCl, saturated NaHCO₃ and brine. The solution was dried over Na₂SO₄ and concentrated to give

14.58 g of residual oil. ^1H NMR (CDCl_3 , ppm ranges are given because of amide rotomers and line broadening) δ 1.36 (s, 9 H), 2.33 (m, 2 H), 2.60 & 2.70 (2s, 3 H), 2.8-3.6 (m, 3 H), 4.94 (m, 2 H), 5.59 (m, 1 H), 6.9-7.4 (m, 3 H). The residue was dissolved in 80 mL of acetone, 40 mL of t-butanol and 40 mL of water. To this solution 1 mL of Osmium tetroxide (4 % solution in water) and 5.15 g (44 mmol) of 4-methylmorpholine N-oxide were added. After stirring for 26 h, the reaction was quenched with approximately 5 g of Na_2SO_3 and concentrated to 25 % of the original volume. The residue was partitioned between water and 1:1 ether (Et_2O), ethyl acetate (EtOAc), the layers were separated and the aqueous layer was extracted with $\text{Et}_2\text{O}:\text{EtOAc}$. Each organic layer was washed with water, brine and dried by filtering through Na_2SO_4 . The filtrate was concentrated to afford the crude diol. A solution of the diol in 120 mL of tetrahydrofuran (THF) and 40 mL of water was treated with 9.42 g (44 mmol) of sodium periodate. After stirring for 2 h, the reaction was diluted with $\text{Et}_2\text{O}:\text{EtOAc}$ and washed with water and brine. The organic layer was dried (Na_2SO_4) and the filtrate was concentrated. The residue was purified by prep LC using 30 % EtOAc /hexane to furnish 11.74 g (83 % yield for three steps) of the title compound as a thick oil. ^1H NMR (CDCl_3 , ppm ranges are given because of amide rotomers and line broadening) δ 1.38 (s, 9 H), 2.69 & 2.75 (2s, 3 H), 2.6-3.65 (m, 5 H), 6.95-7.4 (m, 3 H), 9.67 (s, 1 H).

EXAMPLE 38

1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butoxycarbonyl(methylamino))-butyl]-spiro(1H-indene-1,4'-piperidine).

To a solution of 3.46 g (10 mmol) of 3-(S)-(3,4-dichlorophenyl)-4-(t-butoxycarbonyl-methylamino)butanal (Example 1) in 20 mL of methanol were added 3.11 g (14 mmol) of spiro(1H-indene-1,4'-piperidine) hydrochloride and 3 g of powdered 4 Å molecular sieves. After 15 min a solution of 2.52 g (40 mmol) of NaCNBH_3 in 30 mL of THF was dropwise added. Some gas evolution was observed. After stirring the reaction overnight, the mixture was filtered through a pad

of celite, the reaction flask and the pad were rinsed with methanol. The filtrate was concentrated to approximately 10 ml and the residue was partitioned between saturated NaHCO₃ and Et₂O:EtOAc. The organic layer was washed with water, brine and dried over Na₂SO₄. The filtrate
5 was concentrated and the residue was chromatographed on a flash column using a gradient of 49:49:2 to 98:0:2 EtOAc: Hexane: triethylamine to furnish 4.05 g (79 %) of the title compound as a foam.
¹H NMR (CDCl₃, ppm ranges are given because of amide rotomers and line broadening) δ 1.37 (s, 9 H), 1.5-3.6 (m, 15 H), 2.63 & 2.73 (2 s, 3 H),
10 6.70 (d, 1 H, J=6 Hz), 6.77 (d, 1 H, J=6 Hz), 6.95-7.4 (m, 7 H).

EXAMPLE 39

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dichloro)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

15 Step A: 1'[3-((S)-(3,4-dichlorophenyl))-4-(methylamino)butyl]-spir[1-H-indene-1,4'-piperidine].

Cold trifluoroacetic acid (TFA, 5 mL) and 0.2 mL of anisole were added to 0.565 g (1.1 mmol) of 1'[3-(S)-(3,4-dichlorophenyl)-4-(t-butoxycarbonyl(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)
20 and the mixture was stirred in ice bath until all the foam dissolved. After stirring the resulting solution at room temperature for 30 min, it was concentrated in vacuo. The residue was partitioned between dilute NaOH (ca. 0.5 N) and CH₂Cl₂ and the layers were separated. The organic layer was washed with brine, dried over Na₂SO₄ and
25 concentrated to give 0.523 g of foam which was used in the next step without purification. ¹H NMR (CDCl₃, ppm ranges are given because of amide rotomers and line broadening) δ 1.7-2.7 (m, 10 H), 2.64 (s, 3 H), 2.88 (s, 3 H), 2.9-3.4 (m, 5 H), 3.70 (s, 2H), 6.8-7.4 (m, 7 H).

30 Step B: 1'[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dichloro)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

A solution of 0.105 g (0.55 mmol) of 3,5-dichlorobenzoic acid in 1 mL of CH₂Cl₂ and 2 drops of DMF was treated with 54 µL of oxalyl

chloride. (Gas evolution!) After 20 min the solution was concentrated in vacuo and the residue was mixed with 0.152 g (0.36 mmol) of 1'-[3-((S)-(3,4-dichlorophenyl))-4-(methylamino)butyl]-spiro[1H-indene-1,4'-piperidine obtained from step A, and 0.1 mL (0.71 mmol) of Et₃N in 2 mL of CH₂Cl₂. After 1 h the reaction mixture was diluted with CH₂Cl₂ and washed with saturated NaHCO₃, water, and brine. The CH₂Cl₂ solution was dried over Na₂SO₄, filtered and concentrated. Purification of the residue by prep TLC using 10% methanol-EtOAc afforded 0.18 g (84 % yield) of the title compound as a foam. ¹H NMR (CDCl₃, ppm ranges are given because of amide rotomers and line broadening) δ 1.6-2.4 (m, 10 H), 2.27 (s, 6 H), 2.6-3.9 (m, 10 H), 2.86 (s, 3 H), 6.6-7.5 (m, 10 H). Mass Spectrum (FAB) 589(³⁷Cl + ³⁵Cl isotope), 587(³⁵Cl + ³⁵Cl isotope).

The following compounds were prepared by substituting the required acid chloride for 3,5-dichlorobenzoyl chloride in step B.

EXAMPLE 40

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-chloro)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 555(³⁷Cl + ³⁵Cl isotope), 553(³⁵Cl + ³⁵Cl isotope).

EXAMPLE 41

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-trifluoromethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 589(³⁷Cl + ³⁵Cl isotope), 587(³⁵Cl + ³⁵Cl isotope).

EXAMPLE 42

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-isopropoxy)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 579(³⁷Cl + ³⁵Cl isotope), 577(³⁵ Cl + ³⁵ Cl isotope).

EXAMPLE 43

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-isopropoxy)phenylacetyl-
5 (methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 593(³⁷Cl + ³⁵Cl isotope), 591(³⁵ Cl + ³⁵ Cl isotope).

EXAMPLE 44

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(4-t-butyl)benzoyl-
10 (methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 577(³⁷Cl + ³⁵Cl isotope), 575(³⁵ Cl + ³⁵ Cl isotope).

EXAMPLE 45

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-phenyl)benzoyl-
15 (methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 597(³⁷Cl + ³⁵Cl isotope), 595(³⁵ Cl + ³⁵ Cl isotope).

EXAMPLE 46

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(1-naphthoyl)-(methylamino))butyl]-
20 spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 571(³⁷Cl + ³⁵Cl isotope), 569(³⁵ Cl + ³⁵ Cl isotope).

EXAMPLE 47

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-naphthoyl(methylamino))butyl]-
25 spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 571(^{37}Cl + ^{35}Cl isotope), 569(^{35}Cl + ^{35}Cl isotope).

EXAMPLE 48

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-methyl)benzoyl-
5 (methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 535 (^{37}Cl + ^{35}Cl isotope, M+1), 533 (^{35}Cl + ^{35}Cl isotope, M+1).

EXAMPLE 49

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(4-methyl)benzoyl-
10 (methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 535 (^{37}Cl + ^{35}Cl isotope, M+1), 533(^{35}Cl + ^{35}Cl isotope, M+1).

EXAMPLE 50

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-methyl)benzoyl-
15 (methylamino))butyl]-spiro(1H-indene-1,4'-piperidine).

Mass Spectrum (FAB) 535 (^{37}Cl + ^{35}Cl isotope), 533 (^{35}Cl + ^{35}Cl isotope, M+1).

EXAMPLE 51

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-
20 (methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 549 (^{37}Cl + ^{35}Cl isotope), 547 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 52

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,3-dimethyl)benzoyl-
25 (methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 549 (^{37}Cl + ^{35}Cl isotope), 547 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 53

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,4-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 549 (^{37}Cl + ^{35}Cl isotope), 547 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 54

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,5-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 549 (^{37}Cl + ^{35}Cl isotope), 547 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 55

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,4-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 549 (^{37}Cl + ^{35}Cl isotope), 547 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 56

1'-[3-(S)-(3,4-dichlorophenyl)-4-(trifluoroacetyl(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 512(^{37}Cl + ^{35}Cl isotope), 510(^{35}Cl + ^{35}Cl isotope).

EXAMPLE 57

1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butylcarbonyl(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 501 (^{37}Cl + ^{35}Cl isotope), 499 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 58

1'-[3-(S)-(3,4-dichlorophenyl)-4-(1-adamantanecarbonyl(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 579 ($^{37}\text{Cl} + ^{35}\text{Cl}$ isotope), 577 ($^{35}\text{Cl} + ^{35}\text{Cl}$ isotope).

EXAMPLE 59

1'-[3-(S)-(3,4-dichlorophenyl)-4-(cyclohexanecarbonyl(methyl-
5 amino))butyl]-spiro(1H-indene-1,4'-piperidine)

Mass Spectrum (FAB) 527 ($^{37}\text{Cl} + ^{35}\text{Cl}$ isotope), 525 ($^{35}\text{Cl} + ^{35}\text{Cl}$ isotope).

EXAMPLE 60

10 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-methyl)benzoyl-
(methylamino))butyl]-spiro[indane-1,4'-piperidine]

A mixture of 50 mg (0.093 mmol) of 1'[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-methyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine).(Example 50) and 10 mg of 10% palladium on
15 carbon catalyst in 1 mL of ethanol was hydrogenated on a Parr apparatus. After 30 min the catalyst was filtered on a pad of celite and the filtered solids were washed with EtOAc. The filtrate was concentrated in vacuo and the residue was purified by prep TLC using 2% Et₃N/EtOAc to isolate 35 mg of the title compound as a foam.
20 (Mass Spectrum (FAB) 537 ($^{37}\text{Cl} + ^{35}\text{Cl}$ isotope), 535 ($^{35}\text{Cl} + ^{35}\text{Cl}$ isotope).

EXAMPLE 61

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-
(methylamino))butyl]-spiro[indane-1,4'-piperidine]

25 The title compound was prepared from 1'[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine).(Example 51) by following the procedure of example 24. Mass Spectrum (FAB) 551 ($^{37}\text{Cl} + ^{35}\text{Cl}$ isotope), 549 ($^{35}\text{Cl} + ^{35}\text{Cl}$ isotope).

30

EXAMPLE 62

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-bis(trifluoromethyl)benzoyl(methylamino))butyl)-spiro[(3-indanone)-1,4'-piperidine]

A solution of 98 mg (0.2 mmol) of 3-(S)-(3,4-dichlorophenyl)-4-((3,5-bis(trifluoromethyl)benzoyl(methylamino))butanal and 44 mg (0.22 mmol) of spiro[(3-indanone)1,4'-piperidine in 2 mL of methanol was treated with 4 μ L of HOAC and 0.2 g of powdered molecular sieves. After stirring for 1 h, 0.6 mL of 1 M NaCNBH₃ in THF was dropwise added and the resulting mixture was stirred for 30 min. The reaction was filtered through a pad of celite, the flask and the filtered solids were rinsed with EtOAc. The filtrate was diluted with EtOAc, washed with saturated NaHCO₃, water, brine and dried over Na₂SO₄. The filtrate was concentrated and the residue was chromatographed on a prep TLC plate using 2% Et₃N/EtOAc to furnish 51 mg (38% yield) of the title compound. Mass Spectrum (FAB) (³⁷Cl + ³⁵Cl isotope), (³⁵ Cl + ³⁵ Cl isotope).

The following compounds were synthesized by an analogous procedure using the required aldehyde for the 3-(S)-(3,4-dichlorophenyl)-4-((3,5-bis(trifluoromethyl)benzoyl(methylamino))-butanal.

20

EXAMPLE 63

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine]

Mass Spectrum (FAB) 537 (³⁷Cl + ³⁵Cl isotope), 535 (³⁵ Cl + ³⁵ Cl isotope).

25

EXAMPLE 64

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine]

Mass Spectrum (FAB) 565 (³⁷Cl + ³⁵Cl isotope), 563 (³⁵ Cl + ³⁵ Cl isotope).

30

EXAMPLE 65

1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butoxycarbonyl(methylamino))-butyl]-spiro[(3-indanone)-1,4'-piperidine].

Mass Spectrum (FAB) 533 (^{37}Cl + ^{35}Cl isotope), 531 (^{35}Cl + ^{35}Cl isotope).

5

EXAMPLE 66

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dichloro)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine]

Step A: 1'-[3-(S)-(3,4-dichlorophenyl)-4-(methylamino)butyl]-spiro[(3-indanone)-1,4'-piperidine].

10 Treatment of 0.58 g (1.09 mmol) of 1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butoxycarbonyl(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine] with TFA and anisole according to the procedure of example 39, step A furnished 0.56g of the title compound which was sufficiently pure for use in step B.

15 Step B: 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dichloro)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine]

Reaction of 95 mg (0.22 mmol) of 1'-[3-(S)-(3,4-dichlorophenyl)-4-(methylamino)butyl]-spiro[(3-indanone)-1,4'-piperidine] from step A above, with 3,5-dichlorobenzoyl chloride by the procedure of example 39
20 step B gave the title compound which was purified by prep TLC. Mass Spectrum (FAB) 607 (^{37}Cl + ^{35}Cl isotope), 605 (^{35}Cl + ^{35}Cl isotope).

The following compounds were prepared by substituting the required acid chloride for 3,5-dichlorobenzoyl chloride in step B.

25

EXAMPLE 67

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-chloro-5-methyl)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine]

Mass Spectrum (FAB) 584 (^{37}Cl + ^{35}Cl isotope), 582 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 68

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-fluoro-5-methyl)benzoyl-
5 (methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine]

Mass Spectrum (FAB) 622 (^{37}Cl + ^{35}Cl isotope), 620 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 69

1'-[3-(S)-(3,4-dichlorophenyl)-4-(1-naphthoyl(methylamino))butyl]-
10 spiro[(3-indanone)-1,4'-piperidine]

Mass Spectrum (FAB) 587 (^{37}Cl + ^{35}Cl isotope), 585 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 70

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-
15 (methylamino))butyl]-spiro[(3-hydroxy)indane)-1,4'-piperidine]

A solution of 0.384 g (0.68 mmol) of 1'-[3-(S)-(3,4-dichlorophenyl)-4-
((3,5-dimethyl)benzoyl(methylamino))butyl]-spiro[(3-indanone)-1,4'-
piperidine] (example 64) in 3 mL of methanol was treated with 13 mg
(0.34 mmol) of NaBH_4 . Two additional 13 mg (0.34 mmol) portions of
20 NaBH_4 were added after 45 min intervals and the mixture was stirred
another 45 min. The excess NaBH_4 was destroyed by adding few drops of
10% HCl , diluted with water and the mixture was extracted with EtOAc .
The organic phase was washed with water, brine and dried with
 Na_2SO_4 . The residue after concentration of the filtrate was
25 chromatographed on a flash column to isolate 0.313 g (81% yield) of the
title compound. Mass Spectrum (FAB) 567 (^{37}Cl + ^{35}Cl isotope), 565 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 71

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-
30 (methylamino))butyl]-spiro[(3-acetyloxy)indane)-1,4'-piperidine]

The title compound was obtained by acylation of 1'-[3-(S)-(3,4-dichlorophenyl)-4-((3,5-dimethyl)benzoyl(methylamino))butyl]-spiro[(3-hydroxy)indane]-1,4'-piperidine] (example 70) with acetyl chloride and Et3N in CH2Cl2. Mass Spectrum (FAB) 609 (³⁷Cl + ³⁵Cl isotope), 607 (³⁵Cl + ³⁵Cl isotope).

EXAMPLE 72

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl(methylamino))butyl]-spiro[(3-methylamino-carbonyl-amino)indane]-1,4'-piperidine]

Reductive amination of 3-(S)-(3,4-dichlorophenyl)-4-((3,5-dimethyl)benzoyl(methylamino))butanal (75 mg, 0.2 mmol) and spiro[(3-methylamino-carbonyl-amino)indane]-1,4'-piperidine] (53 mg, 0.22 mmol) by the procedure of example 62 furnished 70 mg (57% yield) of the title compound. Mass Spectrum (FAB) 623 (³⁷Cl + ³⁵Cl isotope), 621 (³⁵Cl + ³⁵Cl isotope).

The following compounds were prepared by reacting the appropriate aldehyde with spiro[(3-ethoxycarbonyl)indane]-1,4'-piperidine] according to the procedure of Example 62.

EXAMPLE 73

1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-bistrifluoromethyl)benzoyl(methylamino))butyl]-spiro[(3-ethoxycarbonyl)indane]-1,4'-piperidine]

Mass Spectrum (FAB) 729(³⁷Cl + ³⁵Cl isotope), 727 (³⁵Cl + ³⁵Cl isotope).

EXAMPLE 74

1'-[3-(S)-(3,4-dichlorophenyl)-4-(benzoyl(methylamino))butyl]-spiro[(3-ethoxycarbonyl)indane]-1,4'-piperidine]

Mass Spectrum (FAB) 593(³⁷Cl + ³⁵Cl isotope), 591(³⁵Cl + ³⁵Cl isotope).

EXAMPLE 75

1'-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(indan-1-one-3,4'-piperidine)

- 5 A mixture of 3-((S)-(3-chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butanal (30 mg, 0.085 mmol) (prepared according to the procedure of Hale, J.J.; Finke, P.E.; MacCoss, M. *Bioorganic & Medicinal Chemistry Letters* **1993**, *3*, 319-322 and Example 13 except using phenylsulfonyl chloride in place of
- 10 the benzoyl chloride in the acylation), spiro(indan-1-one-3,4'-piperidine) (26 mg, 0.128 mmol), 4A molecular sieves (25 mg) and acetic acid (0.008 mL, 0.128 mmol) in THF (1 mL) was stirred at rt for 10 min. Sodium triacetoxyborohydride (36 mg, 0.17 mmol) was then added and the reaction was stirred at rt for 16 h. The mixture was
- 15 poured into a water containing excess sodium carbonate and was extracted twice with ethyl acetate. The organic layers were washed with brine, dried, combined and concentrated in vacuo. The residue was purified by prep TLC using 5% methanol in methylene chloride as eluent to afford the title compound (44 mg).
- 20 Mass Spectrum (NH₃/CI) M+H = 537, 539

EXAMPLE 76

25 1'-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(1-hydroxyindane-3,4'-piperidine)

- To a solution of 1'-(3-((S)-(3-chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-spiro(indan-1-one-3,4'-piperidine) (12 mg, 0.021 mmol) prepared in Example 75 in methanol
- 30 (0.7 mL) was added sodium borohydride (3 x 2 mg, 0.15 mmol) over 2 days until TLC indicated that the reaction was complete. The reaction was then quenched with water and extracted twice with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue

was purified by prep TLC eluting with 5% methanol in methylene chloride to afford the title compound (8.2 mg).

Mass Spectrum (ESI) M+H = 539, 541

5

EXAMPLE 77

1'-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(indane-1,4'-piperidine)

10

A mixture of 3-((S)-(3-chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butanal (35 mg, 0.099 mmol), spiro(indane-1,4'-piperidine) hydrochloride (33 mg, 0.149 mmol), 4A molecular sieves (25 mg) and DIPEA (0.016 mL, 0.149 mmol) in THF (1 mL) was stirred at rt for 10 min. Sodium triacetoxyborohydride (42 mg, 0.20 mmol) was then added and the reaction was stirred at rt for 16 - 40 h. The mixture was poured into a water containing excess sodium carbonate and was extracted three times with ethyl acetate. The organic layers were washed with brine, dried, combined and concentrated in vacuo. The residue was purified by prep TLC using 5% methanol in methylene chloride as eluent to afforded the title compound (36 mg). Mass Spectrum (NH₃/CI) M+H = 523, 525

20

EXAMPLE 78

25

1'-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(6-methoxyindan-1-one-2,4'-piperidine)

30

A mixture of 3-((S)-(3-chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butanal (20 mg, 0.057 mmol), spiro(6-methoxyindan-1-one-2,4'-piperidine) hydrochloride (22 mg, 0.085 mmol), 4A molecular sieves (25 mg) and DIPEA (0.009 mL, 0.085 mmol) in THF (1 mL) was stirred at rt for 10 min. Sodium triacetoxyborohydride (24 mg, 0.114 mmol) was then added and the reaction was stirred at rt for 16 - 40 h. The mixture was poured into a water containing excess sodium carbonate and was extracted three

35

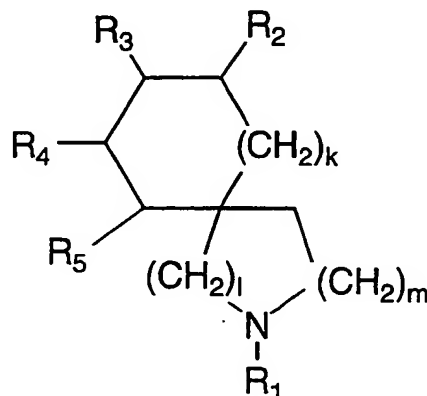
times with ethyl acetate. The organic layers were washed with brine, dried, combined and concentrated in vacuo. The residue was purified by prep TLC using 7% methanol in methylene chloride as eluent to afford the title compound (31 mg).

5 Mass Spectrum (ESI) M+H = 567, 569

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A method for modulation of chemokine receptor activity in a mammal comprising the administration of an effective amount of a compound of formula I:



I

wherein the nitrogen atom expressly shown above is optionally quaternized with C₁₋₄alkyl or phenylC₁₋₄alkyl or is optionally present as the N-oxide (N⁺O⁻), and wherein:

k is 0, 1 or 2;

l and m are each independently 0, 1, 2, 3, 4, or 5, with the proviso that the sum of l + m is equal to 1, 2, 3, 4, or 5;

R₁ is selected from a group consisting of:

- (1) hydrogen,
- (2) linear or branched C₁₋₈ alkyl, linear or branched C₂₋₈ alkenyl, or linear or branched C₂₋₈ alkynyl, wherein the C₁₋₈ alkyl, C₂₋₈ alkenyl or C₂₋₈ alkynyl is optionally mono, di, tri or tetra substituted, the substituents independently selected from:
 - (a) hydroxy,
 - (b) oxo,
 - (c) cyano,
 - (d) halogen, wherein halogen is selected from:

Br, Cl, I, and F,

(e) trifluoromethyl,

(f) phenyl or naphthyl or mono, di or trisubstituted phenyl or naphthyl, the substituents independently selected from

(1') hydroxy,

(2') oxo,

(3') phenyl,

(4') C₁₋₃alkyl,

(5') cyano,

(6') halogen,

(7') trifluoromethyl,

(8') -NR₆COR₇, wherein R₆ and R₇ are

independently selected from:

(a') hydrogen,

(b') C₁₋₆ alkyl, or mono or disubstituted C₁₋₆ alkyl, the substituents independently selected from:

(1'') phenyl,

(2'') hydroxy,

(3'') oxo,

(4'') cyano,

(5'') halogen,

(6'') trifluoromethyl,

(c') phenyl or naphthyl or mono di or trisubstituted phenyl or naphthyl, the substituents independently selected from:

(1'') hydroxy,

(2'') C₁₋₃alkyl,

(3'') cyano,

(4'') halogen,

(5'') trifluoromethyl,

(d') C₁₋₃alkoxy,

or R₆ and R₇ are joined together with the nitrogen to which they are attached to form a 5-, 6-, or 7-membered monocyclic saturated ring containing 1 or

2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and in which the ring is unsubstituted or mono or disubstituted, the substituents independently selected from

- 5 (1") hydroxy,
(2") oxo,
(3") cyano,
(4") halogen,
(5") trifluoromethyl,
10 (9') -NR₆CO₂R₇,
(10') -NR₆CONHR₇,
(11') -NR₆S(O)_jR₇, wherein j is 1 or 2,
(12') -CONR₆R₇,
(13') -COR₆,
15 (14') -CO₂R₆,
(15') -OR₆,
(16') -S(O)_iR₆, wherein i is 0, 1, or 2,
(17') heteroaryl, wherein heteroaryl is selected from
the group consisting of:
20 (1") benzimidazolyl,
(2") benzofuranyl,
(3") benzooxazolyl,
(4") furanyl,
(5") imidazolyl,
25 (6") indolyl,
(7") isooxazolyl,
(8") isothiazolyl,
(9") oxadiazolyl,
(10") oxazolyl,
30 (11") pyrazinyl,
(12") pyrazolyl,
(13") pyridyl,
(14") pyrimidyl,
(15") pyrrolyl,
35 (16") quinolyl,

- (17") tetrazolyl,
(18") thiadiazolyl,
(19") thiazolyl,
(20") thienyl, and
(21") triazolyl,

5

wherein the heteroaryl is unsubstituted or mono di or trisubstituted, the substituents independently selected from:

- (a") hydroxy,
(b") oxo,
(c") cyano,
(d") halogen,
(e") trifluoromethyl,
(g) -NR₆R₇,
(h) -NR₆COR₇,
(i) -NR₆CO₂R₇,
(j) -NR₆CONHR₇,
(k) -NR₆S(O)_jR₇,
(l) -CONR₆R₇,
(m) -COR₆,
(n) -CO₂R₆,
(o) -OR₆,
(p) -S(O)_iR₆,
(q) heteroaryl, wherein heteroaryl is defined above;

10

15

20

25

wherein the nitrogen of definition -NR₆R₇ above is optionally quaternized with C₁₋₄alkyl or phenylC₁₋₄alkyl or is optionally present as the N-oxide (N⁺O⁻);

30

R², R³, R⁴, and R⁵ are independently selected from the group consisting of:

- (1) hydrogen;
(2) hydroxy;
(3) oxo; and

35

- (4) $-NR_6R_7$ or $-NR_6C(O)-NR_6R_7$, wherein the nitrogen of $-NR_6R_7$ is optionally quaternized with C_{1-4} alkyl or phenyl C_{1-4} alkyl or is optionally present as the N-oxide,

5 or R^2 and R^3 , or R^3 and R^4 , together form a carbon-carbon bond, or R^2 and R^3 , or R^3 and R^4 , or R^4 and R^5 are joined to form a ring selected from the group consisting of:

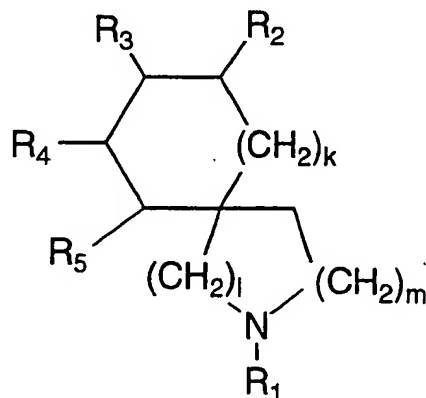
- (a) benzimidazolyl,
- (b) benzofuranyl,
- 10 (c) benzooxazolyl,
- (d) furanyl,
- (e) imidazolyl,
- (f) indolyl,
- (g) isooxazolyl,
- 15 (h) isothiazolyl,
- (i) naphthyl,
- (j) oxadiazolyl,
- (k) oxazolyl,
- (l) phenyl
- 20 (m) pyrazinyl,
- (n) pyrazolyl,
- (o) pyridyl,
- (p) pyrimidyl,
- (q) pyrrolyl,
- 25 (r) quinolyl,
- (s) thiadiazolyl,
- (t) thiazolyl,
- (u) thienyl, and
- (v) triazolyl,

30 and wherein the ring is unsubstituted, mono, di or tri substituted, the substituents selected from:

- (1') C_{1-6} linear or branched alkyl, unsubstituted or mono or disubstituted, the substituents being selected from hydrogen and hydroxy,

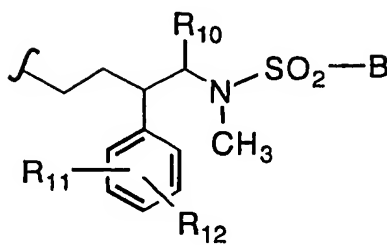
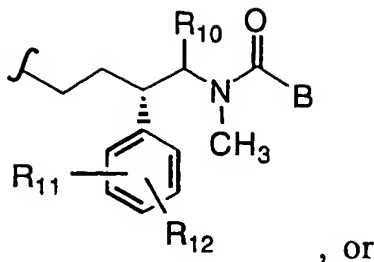
- 5 (2') C₂-6 linear or branched alkenyl,
 (3') hydroxy
 (4') oxo
 (5') -OR₆,
 (6') halogen,
 (7') trifluoromethyl,
 (8') nitro,
 (9') cyano,
 10 (10') -NR⁶R⁷,
 (11') -NR⁶COR⁷,
 (12') -NR₆CO₂R⁷,
 (13') -NR₆CONHR⁷,
 (14') -NR₆S(O)_j-R₇
 15 (15') -CONR⁶R⁷,
 (16') -COR⁶,
 (17') -CO₂R⁶,
 (18') -S(O)_iR₆, and
 (19') heteroaryl, wherein heteroaryl is defined
 above;
 20 X is carbon, or X-R⁵ is oxygen or S-(O)_i;
 and pharmaceutically acceptable salts thereof.

2. The method of Claim 1 wherein the compound is of the Formula II:



II

wherein k is 0 or 1;
 the sum of l + m is 3;
 R₁ is:



5

R₂ and R₃ are independently selected from: hydrogen, hydroxy, oxo, or -NR₆C(O)R₇R₈,

wherein R₆, R₇ and R₈ are independently selected from:

- (a) hydrogen,
- 10 (b) C₁₋₆ alkyl, which is unsubstituted or mono or disubstituted, wherein the substituents on alkyl are independently selected from: hydroxy, halo, trifluoromethyl, C₁₋₃alkyl, and phenyl;
- (c) phenyl, unsubstituted or mono or disubstituted, the
- 15 substituents on phenyl are independently selected from: hydroxy, halo, trifluoromethyl, C₁₋₃alkyl and phenyl;

B is selected from:

- (a) phenyl, naphthyl, mono di or trisubstituted phenyl, and mono
- 20 di or trisubstituted naphthyl, wherein the substituents on phenyl or naphthyl are independently selected from: chloro, methyl, phenyl and CF₃;

(b) $-\text{CH}_2\text{-phenyl}$, or mono or disubstituted $-\text{CH}_2\text{-phenyl}$, wherein the substituents on phenyl are independently selected from: fluoro, chloro, methyl, phenyl or CF_3 ;

5 (c) pyridyl, or mono, di or trisubstituted pyridyl, wherein the substituents on pyridyl are independently selected from: chloro, methyl, phenyl or CF_3 ;

(d) thiophene, or mono or disubstituted thiophene, wherein the substituents on thiophene are independently selected from: chloro, methyl, phenyl or CF_3 ;

10

R_4 and R_5 are joined together to form a ring selected from: thiophene or substituted phenyl, wherein the substituent on phenyl is selected from:

- 15 (a) hydrogen,
(b) $\text{CH}_3\text{O-}$,
(c) $\text{CH}_3\text{SO}_2\text{NH-}$, and
(d) $\text{CH}_3\text{SO}_2\text{-}$;

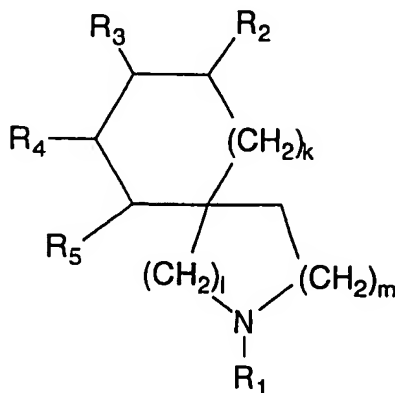
R_{10} is selected from: hydrogen, $\text{C}_1\text{-3alkyl}$, and phenyl;

20

R_{11} and R_{12} are independently selected from:
hydrogen, halogen, methyl, phenyl or CF_3 ;
and pharmaceutically acceptable salts thereof.

25

3. The method of Claim 1 wherein the compound is of the Formula II:



II

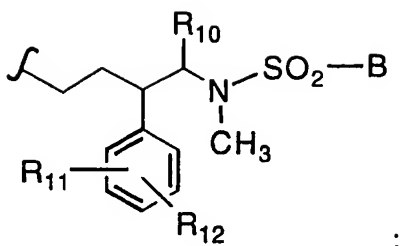
wherein:

k is 0 or 1;

the sum of l + m is 3;

5

R₁ is:



R₂ and R₃ are independently selected from:

hydrogen, hydroxy, oxo, and -NR₆C(O)R₆R₇;

10

B is selected from:

phenyl, mono or disubstituted phenyl, naphthyl, mono or
disubstituted naphthyl, thiophene, and monosubstituted
thiophene wherein the substituent on phenyl, naphthyl or
15 thiophene is selected from: CF₃, CH₃, Cl, F, and Br;

R₄ and R₅ are joined together to form a ring selected from:

thiophene and substituted phenyl, wherein the substituent on
phenyl is selected from:

20

- (a) hydrogen,
- (b) CH₃O-,
- (c) CH₃SO₂NH-, and
- (d) CH₃SO₂-;

25 R₁₀ is hydrogen, C₁-3alkyl or phenyl;

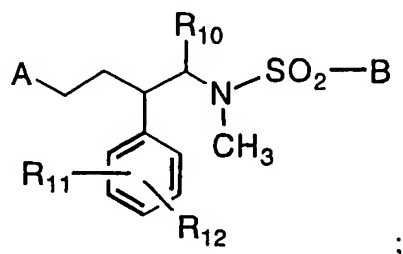
R₁₁ and R₁₂ are independently selected from:

hydrogen, chloro, methyl, phenyl or CF₃;
and pharmaceutically acceptable salts thereof.

4. The method of Claim 3 wherein the compound, B is unsubstituted phenyl, 3-chlorophenyl, 3-fluorophenyl or unsubstituted thiophene.

5

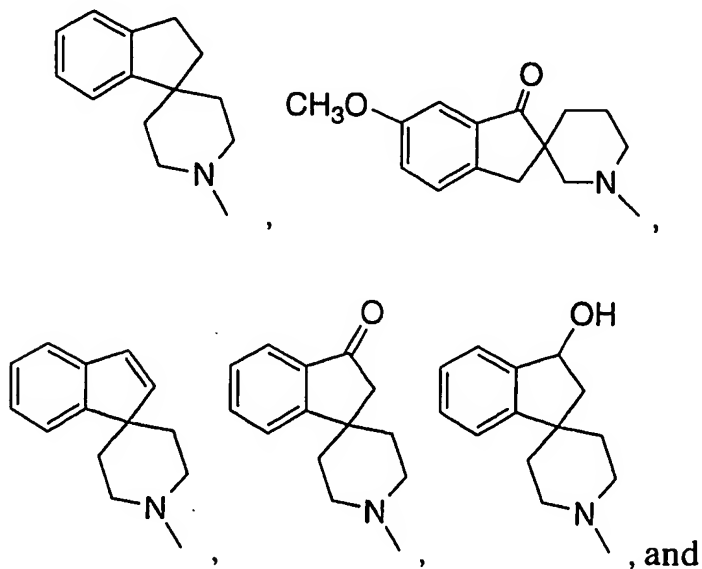
5. The method of Claim 1 wherein the compound is of the Formula III:

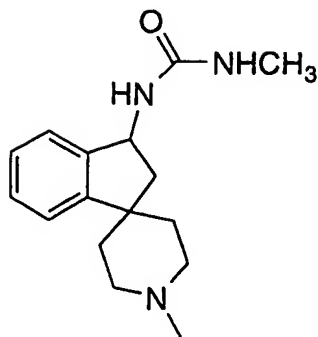


10

III

wherein A is selected from:





B is selected from:

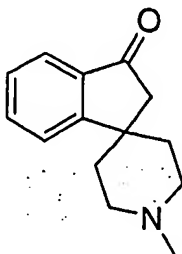
phenyl, mono or disubstituted phenyl, thiophene, and
monosubstituted thiophene wherein the substituent on
5 phenyl or thiophene is selected from:
CF₃, CH₃, Cl, F, and Br;

R₁₁ and R₁₂ are independently selected from:

hydrogen, chloro, methyl, phenyl or CF₃;
10 and pharmaceutically acceptable salts thereof.

6. The method of Claim 5 wherein the compound, B is
unsubstituted phenyl, 3-chlorophenyl, 3-fluorophenyl or unsubstituted
thiophene.

7. The method of Claim 5 wherein the compound, A is:



8. The method of Claim 5 wherein the compound,
R₁₁ and R₁₂ are chloro.

9. The method of Claim 1 wherein the compound is selected from the group consisting of:

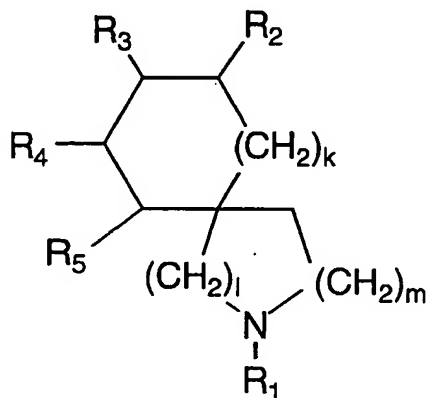
- 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)spiro(1H-indene-1,4'-piperidine);
- 5 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-3,5-bis(trifluoromethyl)benzamido-butyl)spiro(1H-indene-1,4'-piperidine);
- 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)-3,4-dihydro-4-hydroxy-6-methoxy-spiro[2H-1-benzopyran-2,3'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)-10 3,4-dihydro-4-hydroxy-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)spiro(indane-1,4'-piperidine);
- 1'-((1-oxo-(3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)spiro(1H-indene-1,4'-piperidine);
- 15 1'-((3S)-(3,4-dichlorophenyl)-(4)-((N-methyl)benzamido)-pentyl)spiro(1H-indene-1,4'-piperidine);
- 1'-((2)-((3S)-(3,4-dichlorophenyl)-5-(N-methyl)benzamido)pentyl)spiro(1-indane-1,4'-piperidine);
- 1'-((3S)-(3,4-dichlorophenyl)-(4)-((N-methyl)benzamido)octyl)spiro(1H-indene-1,4'-piperidine);
- 20 1'-((4)-((3S)-(3,4-dichlorophenyl)-1-(N-methyl)benzamido)octyl)spiro(1H-indene-1,4'-piperidine);
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)benzene-sulfonamido-butyl) spiro[1H-indene-1,4'-piperidine];
- 25 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)furan-2-carboxamido-butyl) spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)phenoxy-carboxamido-butyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)phenyl-aminocarboxamido-butyl)spiro[1H-indene-1,4'-piperidine];
- 30 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)pyridine-2-carboxamido-butyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)pyridine-3-carboxamido-butyl)spiro[1H-indene-1,4'-piperidine];

- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)pyridine-4-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)benzo-thiophene-2-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 5 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)thiophene-2-acetamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)thiophene-3-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(3-methyl-thiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 10 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(5-methyl-thiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(5-chloro-thiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 15 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(2,3-dibromo-thiophene-5-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butoxycarbonyl(methyl-amino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dichloro)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 20 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-chloro)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-trifluoromethyl)-benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 25 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-isopropoxy)-benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-isopropoxy)-phenylacetyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(4-t-butyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 30 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-phenyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(1-naphthoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);

- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-naphthoyl-(methylamino))butyl)-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-methyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 5 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(4-methyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-methyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 10 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,3-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,4-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 15 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,5-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,4-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 20 1'-[3-(S)-(3,4-dichlorophenyl)-4-(trifluoroacetyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butylcarbonyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(1-adamentanecarbonyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 25 1'-[3-(S)-(3,4-dichlorophenyl)-4-(cyclohexanecarbonyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-methyl)benzoyl-(methylamino))butyl]-spiro[indane-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[indane-1,4'-piperidine];
- 30 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-bistrifluoromethyl)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];

- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butoxycarbonyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 5 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dichloro)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-chloro-5-methyl)benzoyl(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 10 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-fluoro-5-methyl)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(1-naphthoyl(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-hydroxy)indane)-1,4'-piperidine];
- 15 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-acetyloxy)indane)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-methylamino-carbonyl-amino)indane-1,4'-piperidine];
- 20 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-bistrifluoromethyl)benzoyl-(methylamino))butyl]-spiro[(3-ethoxycarbonyl)indane)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(benzoyl(methylamino))-butyl]-spiro[(3-ethoxycarbonyl)indane)-1,4'-piperidine];
- 25 1'-((3-(S)-(3-chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(indan-1-one-3,4'-piperidine);
- 1'-((3-(S)-(3-chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(1-hydroxyindane-3,4'-piperidine);
- 1'-((3-(S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(indane-1,4'-piperidine); and
- 30 1'-((3-(S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(6-methoxyindan-1-one-2,4'-piperidine);
- and pharmaceutically acceptable salts thereof.

10. A method for preventing infection by HIV, treating infection by HIV, delaying of the onset of AIDS, or treating AIDS comprising the administration to a patient of an effective amount of a compound of the formula:



wherein the nitrogen atom expressly shown above is optionally quaternized with C₁₋₄alkyl or phenylC₁₋₄alkyl or is optionally present as the N-oxide (N⁺O⁻), and wherein:

10

k is 0, 1 or 2;

l and m are each independently 0, 1, 2, 3, 4, or 5, with the proviso that the sum of l + m is equal to 1, 2, 3, 4, or 5;

15 R₁ is selected from a group consisting of:

- (1) hydrogen,
- (2) linear or branched C₁₋₈ alkyl, linear or branched C₂₋₈ alkenyl, or linear or branched C₂₋₈ alkynyl, wherein the C₁₋₈ alkyl, C₂₋₈ alkenyl or C₂₋₈ alkynyl is optionally mono, di, tri or tetra substituted, the substituents independently selected from:
 - (a) hydroxy,
 - (b) oxo,
 - (c) cyano,
 - (d) halogen, wherein halogen is selected from: Br, Cl, I, and F,

20

25

(e) trifluoromethyl,
(f) phenyl or naphthyl or mono, di or trisubstituted
phenyl or naphthyl, the substituents independently selected
from

5

(1') hydroxy,

(2') oxo,

(3') phenyl,

(4') C₁-3alkyl,

(5') cyano,

10

(6') halogen,

(7') trifluoromethyl,

(8') -NR₆COR₇, wherein R₆ and R₇ are

independently selected from:

(a') hydrogen,

15

(b') C₁-6 alkyl, or mono or disubstituted C₁-6 alkyl,
the substituents independently selected from:

(1'') phenyl,

(2'') hydroxy,

(3'') oxo,

20

(4'') cyano,

(5'') halogen,

(6'') trifluoromethyl,

(c') phenyl or naphthyl or mono di or trisubstituted
phenyl or naphthyl, the substituents independently
selected from:

25

(1'') hydroxy,

(2'') C₁-3alkyl,

(3'') cyano,

(4'') halogen,

30

(5'') trifluoromethyl,

(d') C₁-3alkyloxy,

or R₆ and R₇ are joined together with the nitrogen to
which they are attached to form a 5-, 6-, or 7-
membered monocyclic saturated ring containing 1 or
2 heteroatoms independently selected from nitrogen,

35

oxygen, and sulfur, and in which the ring is unsubstituted or mono or disubstituted, the substituents independently selected from

- 5 (1") hydroxy,
(2") oxo,
(3") cyano,
(4") halogen,
(5") trifluoromethyl,
(9') -NR₆CO₂R₇,
10 (10') -NR₆CONHR₇,
(11') -NR₆S(O)_jR₇, wherein j is 1 or 2,
(12') -CONR₆R₇,
(13') -COR₆,
(14') -CO₂R₆,
15 (15') -OR₆,
(16') -S(O)_iR₆, wherein i is 0, 1, or 2,
(17') heteroaryl, wherein heteroaryl is selected from
the group consisting of:
20 (1") benzimidazolyl,
(2") benzofuranyl,
(3") benzooxazolyl,
(4") furanyl,
(5") imidazolyl,
(6") indolyl,
25 (7") isooxazolyl,
(8") isothiazolyl,
(9") oxadiazolyl,
(10") oxazolyl,
(11") pyrazinyl,
30 (12") pyrazolyl,
(13") pyridyl,
(14") pyrimidyl,
(15") pyrrolyl,
(16") quinolyl,
35 (17") tetrazolyl,

(18") thiadiazolyl,

(19") thiazolyl,

(20") thienyl, and

(21") triazolyl,

5 wherein the heteroaryl is unsubstituted or mono di or trisubstituted, the substituents independently selected from:

(a") hydroxy,

(b") oxo,

10 (c") cyano,

(d") halogen,

(e") trifluoromethyl,

(g) -NR₆R₇,

(h) -NR₆COR₇,

15 (i) -NR₆CO₂R₇,

(j) -NR₆CONHR₇,

(k) -NR₆S(O)_jR₇,

(l) -CONR₆R₇,

(m) -COR₆,

20 (n) -CO₂R₆,

(o) -OR₆,

(p) -S(O)_iR₆,

(q) heteroaryl, wherein heteroaryl is defined above;

25

wherein the nitrogen of definition -NR₆R₇ above is optionally quaternized with C₁₋₄alkyl or phenylC₁₋₄alkyl or is optionally present as the N-oxide (N⁺O⁻);

30 R², R³, R⁴, and R⁵ are independently selected from the group consisting of:

(1) hydrogen;

(2) hydroxy;

(3) oxo; and

- (4) -NR₆R₇ or -NR₆C(O)-NR₆R₇, wherein the nitrogen of -NR₆R₇ is optionally quaternized with C₁₋₄alkyl or phenylC₁₋₄alkyl or is optionally present as the N-oxide,

5 or R² and R³, or R³ and R⁴, together form a carbon-carbon bond, or R² and R³, or R³ and R⁴, or R⁴ and R⁵ are joined to form a ring selected from the group consisting of:

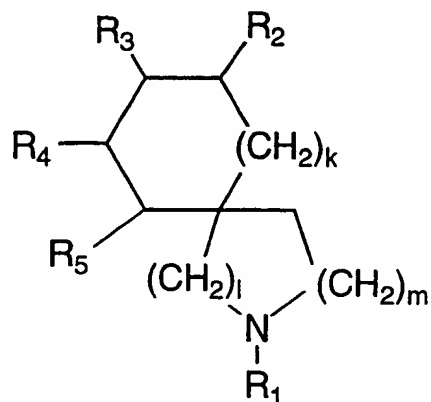
- (a) benzimidazolyl,
- (b) benzofuranyl,
- 10 (c) benzooxazolyl,
- (d) furanyl,
- (e) imidazolyl,
- (f) indolyl,
- (g) isooxazolyl,
- 15 (h) isothiazolyl,
- (i) naphthyl,
- (j) oxadiazolyl,
- (k) oxazolyl,
- (l) phenyl
- 20 (m) pyrazinyl,
- (n) pyrazolyl,
- (o) pyridyl,
- (p) pyrimidyl,
- (q) pyrrolyl,
- 25 (r) quinolyl,
- (s) thiadiazolyl,
- (t) thiazolyl,
- (u) thienyl, and
- (v) triazolyl,

30 and wherein the ring is unsubstituted, mono, di or tri substituted, the substituents selected from:

- (1') C₁₋₆ linear or branched alkyl, unsubstituted or mono or disubstituted, the substituents being selected from hydrogen and hydroxy,

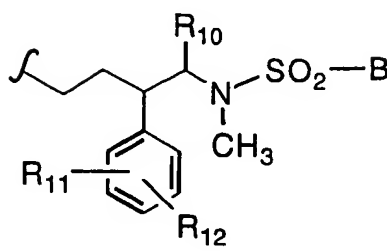
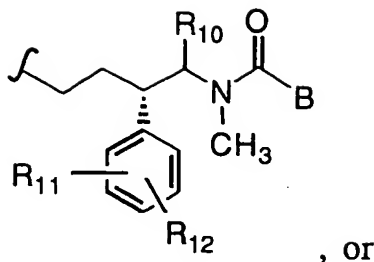
- 5 (2') C₂₋₆ linear or branched alkenyl,
 (3') hydroxy
 (4') oxo
 (5') -OR₆,
 (6') halogen,
 (7') trifluoromethyl,
 (8') nitro,
 (9') cyano,
 10 (10') -NR⁶R⁷,
 (11') -NR⁶COR⁷,
 (12') -NR₆CO₂R⁷,
 (13') -NR₆CONHR⁷,
 (14') -NR₆S(O)_j-R⁷
 (15') -CONR⁶R⁷,
 15 (16') -COR⁶,
 (17') -CO₂R⁶,
 (18') -S(O)_jR₆, and
 (19') heteroaryl, wherein heteroaryl is defined
 above;
 20 X is carbon, or X-R⁵ is oxygen or S-(O)_i;
 and pharmaceutically acceptable salts thereof.

11. The method of Claim 10 wherein the compound is of the Formula II:



II

wherein k is 0 or 1;
 the sum of l + m is 3;
 R₁ is:



5

R₂ and R₃ are independently selected from: hydrogen, hydroxy, oxo, or -NR₆C(O)R₇R₈,

wherein R₆, R₇ and R₈ are independently selected from:

- (a) hydrogen,
- 10 (b) C₁-6 alkyl, which is unsubstituted or mono or disubstituted,
 wherein the substituents on alkyl are independently
 selected from: hydroxy, halo, trifluoromethyl, C₁-3alkyl,
 and phenyl;
- 15 (c) phenyl, unsubstituted or mono or disubstituted, the
 substituents on phenyl are independently selected from:
 hydroxy, halo, trifluoromethyl, C₁-3alkyl and phenyl;

B is selected from:

- 20 (a) phenyl, naphthyl, mono di or trisubstituted phenyl, and mono
 di or trisubstituted naphthyl, wherein the substituents on
 phenyl or naphthyl are independently selected from:
 chloro, methyl, phenyl and CF₃;

(b) $-\text{CH}_2\text{-phenyl}$, or mono or disubstituted $-\text{CH}_2\text{-phenyl}$, wherein the substituents on phenyl are independently selected from: fluoro, chloro, methyl, phenyl or CF_3 ;

5 (c) pyridyl, or mono, di or trisubstituted pyridyl, wherein the substituents on pyridyl are independently selected from: chloro, methyl, phenyl or CF_3 ;

(d) thiophene, or mono or disubstituted thiophene, wherein the substituents on thiophene are independently selected from: chloro, methyl, phenyl or CF_3 ;

10

R_4 and R_5 are joined together to form a ring selected from: thiophene or substituted phenyl, wherein the substituent on phenyl is selected from:

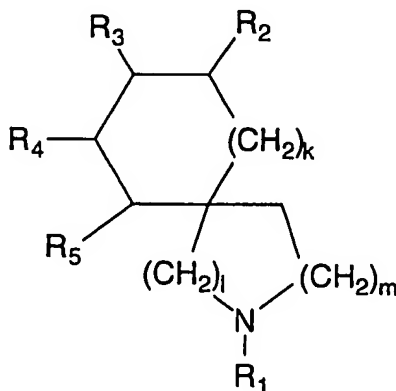
- 15 (a) hydrogen,
(b) $\text{CH}_3\text{O-}$,
(c) $\text{CH}_3\text{SO}_2\text{NH-}$, and
(d) $\text{CH}_3\text{SO}_2\text{-}$;

R_{10} is selected from: hydrogen, $\text{C}_{1-3}\text{alkyl}$, and phenyl;

20

R_{11} and R_{12} are independently selected from:
hydrogen, halogen, methyl, phenyl or CF_3 ,
and pharmaceutically acceptable salts thereof.

25 12. The method of Claim 10 wherein the compound is of the Formula II:



II

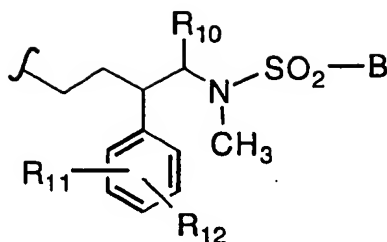
wherein:

k is 0 or 1;

the sum of l + m is 3;

5

R₁ is:



R₂ and R₃ are independently selected from:

hydrogen, hydroxy, oxo, and -NR₆C(O)R₆R₇;

10

B is selected from:

phenyl, mono or disubstituted phenyl, naphthyl, mono or disubstituted naphthyl, thiophene, and monosubstituted thiophene wherein the substituent on phenyl, naphthyl or thiophene is selected from: CF₃, CH₃, Cl, F, and Br;

15

R₄ and R₅ are joined together to form a ring selected from:

thiophene and substituted phenyl, wherein the substituent on phenyl is selected from:

20

- (a) hydrogen,
- (b) CH₃O-,
- (c) CH₃SO₂NH-, and
- (d) CH₃SO₂-;

25

R₁₀ is hydrogen, C₁-3alkyl or phenyl;

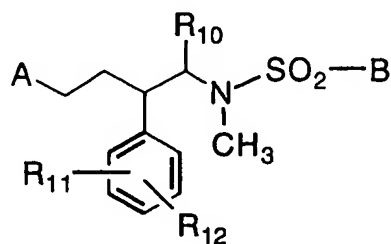
R₁₁ and R₁₂ are independently selected from:

hydrogen, chloro, methyl, phenyl or CF₃;
and pharmaceutically acceptable salts thereof.

13. The method of Claim 12 wherein the compound, B is unsubstituted phenyl, 3-chlorophenyl, 3-fluorophenyl or unsubstituted thiophene.

5

14. The method of Claim 10 wherein the compound is of the Formula III:

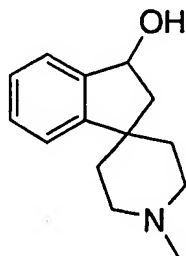
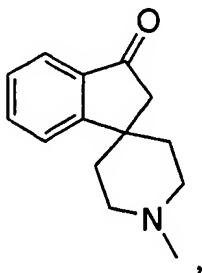
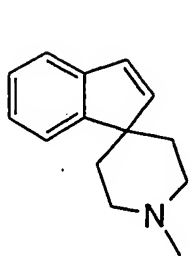
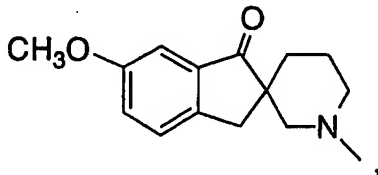
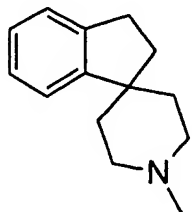


;

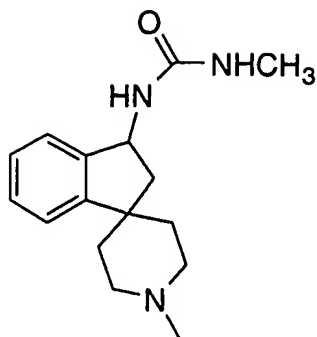
10

III

wherein A is selected from:



, and



B is selected from:

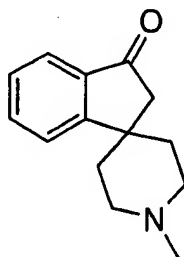
- phenyl, mono or disubstituted phenyl, thiophene, and
monosubstituted thiophene wherein the substituent on
5 phenyl or thiophene is selected from:
CF₃, CH₃, Cl, F, and Br;

R₁₁ and R₁₂ are independently selected from:

- hydrogen, chloro, methyl, phenyl or CF₃;
10 and pharmaceutically acceptable salts thereof.

15 15. The method of Claim 14 wherein the compound, B is
unsubstituted phenyl, 3-chlorophenyl, 3-fluorophenyl or unsubstituted
thiophene.

16. The method of Claim 14 wherein the compound, A is:



17. The method of Claim 14 wherein the compound,
R₁₁ and R₁₂ are chloro.

20

18. The method of Claim 10 wherein the compound is selected from the group consisting of:

- 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)spiro(1H-indene-1,4'-piperidine);
- 5 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-3,5-bis(trifluoromethyl)benzamido-butyl)spiro(1H-indene-1,4'-piperidine);
- 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)-3,4-dihydro-4-hydroxy-6-methoxy-spiro[2H-1-benzopyran-2,3'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)-3,4-dihydro-4-hydroxy-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperidine];
- 10 1'-((3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)spiro(indane-1,4'-piperidine);
- 1'-((1-oxo-(3S)-(3,4-dichlorophenyl)-4-(N-methyl)benzamido-butyl)spiro(1H-indene-1,4'-piperidine);
- 15 1'-((3S)-(3,4-dichlorophenyl)-(4)-((N-methyl)benzamido)-pentyl)spiro(1H-indene-1,4'-piperidine);
- 1'-((2)-((3S)-(3,4-dichlorophenyl)-5-(N-methyl)benzamido)pentyl)spiro(1-indane-1,4'-piperidine);
- 1'-((3S)-(3,4-dichlorophenyl)-(4)-((N-methyl)benzamido)octyl)spiro(1H-indene-1,4'-piperidine);
- 20 1'-((4)-((3S)-(3,4-dichlorophenyl)-1-(N-methyl)benzamido)octyl)spiro(1H-indene-1,4'-piperidine);
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)benzene-sulfonamido-butyl) spiro[1H-indene-1,4'-piperidine];
- 25 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)furan-2-carboxamido-butyl) spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)phenoxy-carboxamido-butyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)phenyl-aminocarboxamido-butyl)spiro[1H-indene-1,4'-piperidine];
- 30 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)pyridine-2-carboxamido-butyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)pyridine-3-carboxamido-butyl)spiro[1H-indene-1,4'-piperidine];

- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)pyridine-4-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)benzo-thiophene-2-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 5 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)thiophene-2-acetamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)thiophene-3-carboxamidobutyl)spiro[1H-indene-1,4'-piperidine];
- 10 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(3-methylthiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(5-methylthiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(5-chlorothiophene-2-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 15 1'-((3S)-(3,4-dichlorophenyl)-4-((N-methyl)-(2,3-dibromothiophene-5-carboxamido)butyl)spiro[1H-indene-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butoxycarbonyl(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dichloro)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 20 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-chloro)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-trifluoromethyl)-benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 25 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-isopropoxy)-benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-isopropoxy)-phenylacetyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(4-t-butyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 30 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-phenyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(1-naphthoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);

- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-naphthoyl-(methylamino))butyl)-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2-methyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 5 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(4-methyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-methyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 10 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,3-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,4-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 15 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,5-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(2,4-dimethyl)benzoyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 20 1'-[3-(S)-(3,4-dichlorophenyl)-4-(trifluoroacetyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butylcarbonyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(1-adamentanecarbonyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 25 1'-[3-(S)-(3,4-dichlorophenyl)-4-(cyclohexanecarbonyl-(methylamino))butyl]-spiro(1H-indene-1,4'-piperidine);
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-methyl)benzoyl-(methylamino))butyl]-spiro[indane-1,4'-piperidine];
- 30 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[indane-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-bistrifluoromethyl)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];

- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(t-butoxycarbonyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 5 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dichloro)benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-chloro-5-methyl)-benzoyl(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3-fluoro-5-methyl)-benzoyl-(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 10 1'-[3-(S)-(3,4-dichlorophenyl)-4-(1-naphthoyl(methylamino))butyl]-spiro[(3-indanone)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-hydroxy)indane)-1,4'-piperidine];
- 15 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-acetyloxy)indane)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethyl)benzoyl-(methylamino))butyl]-spiro[(3-methylamino-carbonyl-amino)indane)-1,4'-piperidine];
- 20 1'-[3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-bistrifluoromethyl)benzoyl-(methylamino))butyl]-spiro[(3-ethoxycarbonyl)indane)-1,4'-piperidine];
- 1'-[3-(S)-(3,4-dichlorophenyl)-4-(benzoyl(methylamino))-butyl]-spiro[(3-ethoxycarbonyl)indane)-1,4'-piperidine];
- 25 1'-(3-((S)-(3-chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(indan-1-one-3,4'-piperidine);
- 1'-(3-((S)-(3-chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(1-hydroxyindane-3,4'-piperidine);
- 1'-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(indane-1,4'-piperidine); and
- 30 1'-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))-butyl)-spiro(6-methoxyindan-1-one-2,4'-piperidine);
- and pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/23093

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/33, 31/395, 31/41, 31/435, 31/55

US CL : 514/ 183, 210, 212, 213, 278, 409

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/ 183, 210, 212, 213, 278, 409

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| Y | Chem. abstr. Vol. 111, No. 17, 23 October 1989 (Columbus, OH, USA), page 79, column 1, abstract No. 111:146934q, WIEDERMANN et. al. 'In vitro human polymorphonuclear leukocyte chemokinesis and human monocyte chemotaxis are different activities of aminoterminal and carboxyterminal substance P' Naunyn-Schmiedeberg's Arch. Pharmacol. 1989, 340(2), 185-90 (Eng). See entire article. | 1-9 |
| Y | Chem. abstr. Vol. 123, No. 5, 31 July 1995, (Columbus, OH, USA), pages 904-905, column 2, the abstract No. 123:55696v, HALE et al. 'Preparation of spiro-substituted azcycles as tachykinin receptor antagonists' PCT INT. APPL. WO 94 17,045 04 August 1994. See entire article. | 1-17 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|---|--|
| * Special categories of cited documents: | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A* document defining the general state of the art which is not considered to be of particular relevance | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *E* earlier document published on or after the international filing date | *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *Z* document member of the same patent family |
| *O* document referring to an oral disclosure, use, exhibition or other means | |
| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

05 MARCH 1998

Date of mailing of the international search report

08 APR 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/US97/23093

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| Y | Chem. abstr. vol. 123, No. 11, 11 September 1995 (Columbus, OH, USA), page 247, column 2, the abstract No. 123:133809a, KIM et al. 'Migration and proliferation of guinea pig and human airway epithelial cells in response to tachykinins' Am. J. Physiol., 1995, 269(1,Pt. 1), L119-L126 (Eng). See entire article. | 1-9 |
| Y | Chem. abstr. Vol. 123, No. 13, 25 September 1995 (Columbus, OH, USA) page 1080, column 2, abstract No. 123:169671p, MACCOSS et al. 'Preparation of spirocyclic compounds as neurokinin antagonists' PCT Int. Appl. WO 94 29,309, 22 Dec. 1994. See entire article. | 1-17 |
| Y | HIRSCHMANN 'Peptide related research as a vehicle towards chemical and biological understanding' (Eng). In: Books of Abstracts, 213TH ACS National Meeting, 13-17 April, 1997 (San Francisco, USA), MEDI-001. See entire article. | 10-17 |
| Y,P | Chem. Abstr. Vol. 127, No. 1, 07 July 1997 (Columbus, OH, USA) page 606, column 2, abstract No. 127:5325k, YAO 'the rational approach to the design and synthesis of NK-1 receptor antagonist and HIV-1 protease inhibitors (Immune deficiency, selective peptidal somatostatin peptidomimetics)' Diss. Abst. Int. B, 1997, 57(11) 6946. See entire article. | 10-17 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/23093

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

CAS--structure

DIALOG, APS-- neurokinin, tachykinin, nk1, nk2, nk3, nka, nkb, chemokine, HIV, immunodeficiency

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1.

Group I, claims 1-9, drawn to method of modulating chemokine receptor activity.

Group II, claims 10-18, drawn to method of preventing, treating HIV infection or delaying onset or treating AIDS.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because the method for group I and for group II are not related. Under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The method of modulating a biological receptor comprises administering to a mammal in need thereof a receptor affinity effective amount of a known compound of claim 1.

The method of preventing, treating HIV infection or delaying onset or treating AIDS comprises administering to a "patient" an antiviral or therapeutical effective amount of a known compound of claim 10.

The subject, dosage and conditions being ameliorated in group I or group II are independent and distinct from each other without any cause/effect relationship. Therefore, the two process of using the products are independent inventive concepts for which independent searches are required.